Leiber 1953

CAUSES AND TREATMENT OF ABDOMINAL ADHESIONS

LIBRARY
SAN FRANCISCO

A. L. MYBURGH

CAUSES AND TREATMENT OF ABDOMINAL ADHESIONS.

CAUSES AND TREATMENT OF ABDOMINAL ADHESIONS

PROEFSCHRIFT TER VERKRIJGING VAN DE GRAAD VAN DOCTOR IN DE GENEESKUNDE AAN DE RIJKS-UNIVERSITEIT TE LEIDEN, OP GEZAG VAN DE RECTOR MAGNIFICUS, MR J. M. VAN BEMMELEN, HOOGLERAAR IN DE FACULTEIT DER RECHTSGELEERDHEID, TEGEN DE BEDENKINGEN VAN DE FACULTEIT DER GENEESKUNDE TE VERDEDIGEN OP WOENSDAG 21 OCTOBER 1953 TE 14 UUR

DOOR

ALBERT LIONEL MYBURGH

GEBOREN TE VREDENBURG IN 1911
(ZUID-AFRIKA)

EDUARD IJDO N.V. — LEIDEN

Promotor: Prof. Dr W. F. Suermondt.

TO MY FATHER AND MOTHER.

The following Authors and Publishers or both have kindly given their permission to use information, charts, tables or photographs in this Thesis. To them I am very grateful.

Krook, S. S. (1947) Acta Chir. Scand. Supplement **125**: P. 13.
(P. E. Norstedt and Söner, Tryckerigatan 2, Stockholm.)

Burgess, A. H. (1929) The Lancet, April 27.
(The Lancet, 7 Adam St. Adelphi, London W. $C._2$.)

Da Costa, (1931) Modern Surgery Ed. **10**. P. 903.
(W. B. Saunders Co, West Washington Sq., Philad. 5.)

McGregor, A. Lee, (1949) Ed. **4**, P. 52.
(John Wright & Sons Ltd., Bristol.)

Johnson, H. L. (1928) New Eng. J. M. **119**, 661.
(New Eng. J. Med. 8 Fenway, Boston 15. U. S. A.)

Hamilton, Boyd & Mossman (1952) Human Embryology Ed. **2**, P. 214.
(W. Heffer & Sons Ltd., Cambridge.)

Crutcher et al. (1943) Ann. Surg. **117**, P. 677.
(J. B. Lippincott Co., Philad. 5. U. S. A.)

Yardumian, K., & Cooper D. H. (1934) Arch. Surg. **29**, P. 564.
(The American Med. Ass. 535 N. Dearborn St., Chicago, 10.)

Boys, F., (1942) Surgery **2**, P. 118.
(C.V. Mosby Co., 3207 Washington Blvd., St Louis 3).

Chandy, J., (1950) Arch. Surg. **60**, P. 1511.
(The Am. Med. Ass., 535 N. Dearborn St., Chicago 10.)

Scheinberg, S. R., & Saltzstein, H. C., (1951) Arch. Surg. **63**, P. 413.
(Amer. Med. Ass., 535 N. Dearborn St., Chicago, 10.)

Baar, F. (1953). B. M. J. May, 23, 1146.
(B. M. J. Tavistock Sq., London.)

I regret to state that according to information Prof. A. H. Burgess, Dr D. H. Cooper & Dr daCosta are deceased.

CONTENTS.

pags.

CHAPTER I.

Introduction 1

CHAPTER II.

The Evolution and History of Adhesions 3

CHAPTER III.

The Literature and History of Adhesions 6

CHAPTER IV.

The Peritoneum; its Development, Anatomy and Surgical Anatomy 15

CHAPTER V.

The Physiology, Applied Physiology, Sensitivity of the Peritoneum, and the Applied Physiology of Intraperitoneal Adhesions 33

CHAPTER VI.

The Recognition of Intestinal Obstruction 44

CHAPTER VII.

Histological Genesis and Frequency of Adhesions 50

CHAPTER VIII.

Modern Studies and Views on Adhesions.

A. Causation and Prevention of Adhesions 64

B. Amniotic Fluid 66

pags.

C. Digestive Ferments, Pepsin and Trypsin 68
D. Papaine 74
E. Streptokinase and Streptodornase 76
F. Reperitonealization 78
G. Sulphanilamides 83
H. Talc effects 91
I. Heparin 98
J. Cortisone 99
K. Hyaluronidase 108

CHAPTER IX.

Author's own work and findings 111

CHAPTER X.

Discussion 160
Summary 179
Bibliography 180

CHAPTER I.

INTRODUCTION.

The formation of abdominal adhesions is a protective process of nature in some cases; it is also the end result of abliterated disease and is frequently initiated by our erroneous surgical methods.

Many surgeons and pathologists have endeavoured to solve the surgical problem created by the formation of these adhesions. The aim of this thesis is an attempt to correlate useful facts from valuable literature in this field, with original work on the subject.

Extensive interest has been shown in adhesions and their prevention recently, more so than in the past. Although it remains with the most experienced to judge, it seems as if this problem is much nearer to being solved.

There seems to be little doubt that the answer is going to be a substance which most closely approximates nature's method. From the work of authentic authors it will be seen later that a proteolytic enzyme or something similar is secreted in the presence of leucocytosis. It therefore seems most likely that a product taken from body tissues as an organic substance or chemical, or even better, *an enzyme* could conform to our requirements.

Previous studies on this subject from the earliest times to the present day will be reviewed in detail.

A knowledge of the anatomy of the peritoneum and its development and physiology is essential to a study of this kind and so will also be included in detail.

The writer's own experimental work on this subject will then be described. Finally the conclusions reached as a result of this work will be discussed.

Before the previous literature on this subject is reviewed, a brief classification of the various methods used in an attempt to prevent adhesions is given as follows:

1. *Protection of the peritoneum from injury* whether traumatic, thermal or chemical and abstention from the introduction of particles such as talcum powder and foreign bodies like rubber drains.

2. *Prevention of solidification of the exudate* that occurs over traumatized areas of serosa; this could be achieved if adjacent traumatized areas of peritoneum were kept apart. Amniotic fluid was used for this purpose with promising results, but lubricants and membranes failed. To interfere with coagulation, Chandy tried heparin in 1950.

3. *Interference with the formation of fibrin* in the early stages was attempted by the use of enzymes and digestants. Pepsin (Yardumian and Cooper 1934), trypsin, and Papain (Ochsner and Garside 1934) the enzyme from the unripe fruit of the papaw tree, were the most successful methods.

4. *Inhibition of fibrobrastic reaction.*

   In 1951 Scheinberg and Saltzstein used cortisone after it had been observed that adhesions were not formed in patients while treated with cortisone for other complaints. (eg rheumatoid arthritis). They were successful with their acurate doses given, but criticised by authors who proved experimentally that cortisone delayed the healing of wounds, as will be described later.

5. *Promoting rapid absorption of the exudate, and dissolving the fibrin.*

   Conolly and Richards (1951) used the enzyme Hyaluronidase, and this work is of great importance in the aim at solution of our problem of abdominal adhesions.

   In June 1952, not yet having read of this important work, the writer began his experiments on rabbits, using a similar British drug "Hyaluronidase" (Hyalase).

CHAPTER II.

THE EVOLUTION AND HISTORY OF ADHESIONS.

Carson (1923) wrote a paper on the Evolution of the modern treatment of Peritonitis. He quotes John Hunter (1728—1793) who wrote about Peritonitis. Hunter wrote a great deal, and all his volumes are to be found at the Royal College of Surgeons in London.

In his first volume, letters of his time are attached to the inside cover and also an original piece of his coffin cloth.

On adhesive inflammation he wrote: "If the actions of adhesive inflammation be allowed to extend themselves, it would prove more hurtful than any good that could arise from it; hence there are natural obstructions to extending which we shall first consider." He said that inflammation in internal surfaces extended by "Continuous sympathy."

On the effects of adhesions he wrote: "These effects are very slight even when the inflammation arises from violence; but the effects of those inflammations which are indolent in their progress are still more trifling in the constitution. This arises from the slowness of the alteration produced in the past, as it were, insensibly stealing on the constitution."

Hunter was interested in the Peritoneum. He wrote "That the inflammation of the peritoneum rises from the stimulus of imperfection is also evident, because if a man is wounded in the belly with a sword, which has also wounded one of the intestines, if the wound in the abdomen is closed and unites by first intention, the wound in the intestine will unite with some parts with which it comes in contact, either by extravasated blood or the adhesive inflammation, and no other trouble will ensue, because the stimulus of imperfection has not been given.

But if a man is wounded in the belly and there is no wound of the viscera, yet if the wound is kept from healing by first

intention, the whole peritoneum becomes inflamed immediately — not from the spreading of inflammation by the continuity of surface, but the consciousness of imperfection in the membrane itself by which the whole is brought into the same action."

He also recognised puerperal fever as a true peritonitis, a conclusion that preceeded Bichat's work by some thirty years.

Carson (1923) writes that there is little direct evidence obtained from prehistoric sources. The ancient Egyptians deposited the internal organs of the dead in four canopic jars, but Prof. Elliot Smith, and Prof. Wood Jones in their "Archaeological Survey of Nubia" (Carson 1923) could only report one case of adhesions due to old peritonitis, and that not even in a jar, but in the pelvis of a woman buried in the cemetary No. 2 on Hesa. There is nothing on acute abdominal disorders in the Ebers Papyrus (1500 B. C.), but in the fragmentory tablets of the library of Assur-Bani-Pal, at Nineveh (600 B. C.), there are instructions for treating Colic. It is certain that abdominal disorders were well known in Egypt, for Herodotus (Carson 1923) states that medicine was practised upon a plan of separation. "Some cure diseases of the eye, others of the head, others again of the teeth, others of the intestines." According to Carson there is in the Wellcome Museum (London) an excellent specimen of a clay votive offering found on the banks of the Tiber by a Mr. Thompson, who demonstrated it to H. W. Carson. It is said to look exactly like the post mortem appearances of the abdominal cavity of a patient who died of diffuse peritonitis, and is life size. Thompson dates it about A. D. 200.

This specimen, on investigation, has been removed from the Burrows Wellcome Museum, and is possibly to be seen at 28 Portman Square, London.

In those early mediaeval times there were no post-mortems and symptoms were more important than signs. Mystery was soon attached to sudden, painful, severe and fatal illness; illnesses such as peritonitis, obstruction or perforation and appendicitis. When the deceased was a personage of importance, there were whispers of foul play. Carson thinks that William the Conqueror possibly died of peritonitis following rupture of the intestine and that King Stephen probably died of the "iliac passion." This might have been any acute abdominal disorder

as for instance appendicitis, obstruction of bowel or stangulated hernia. This "Passio iliaca" was also known as "ileus" and "miserere." In the Rosa Anglica 1314, John of Goddesden differentiates between the "iliac passion" (peritonitis), the "colic passion" (obstruction) and the renal passion. He relates that the iliac passion is accompanied by frequent vomiting, hardness of the abdomen, and acute pain as if a gimlet were boring through the intestine. Enemata and fomentations were used as treatment. Praxagoras of Cos, 100 B. C. treated the vomiting by giving emetics until faeculent vomiting occurred. (Carson 1923.)

According to Carson little advance was made until the 17th Century when Thomas Willis (1621—75) described the colic passion and disagreed with others that it was to be counted among the distempers of the brain and nervous stock. Willis also found that purgatives made the disease worse.

In 1759 Heister reported the first case of appendix abscess, which he discovered in 1711, when doing a post-mortem on a malefactor in the public theatre of Altdorf. (Carson 1923.)

In 1759 a case of appendicitis was reported in a man of 45 by Mestivier. The case was admitted to Hôpital St Andre de Bordeaux with a large abscess in the right iliac fossa. One pint of offensive pus was removed by incision and a pin was found in the appendix at post-mortem. A few more cases were reported in France about this time, and in 1812 Parkinson, a pupil of John Hunter reported the first case in England (Carson 1923).

From this literature we can see that adhesive inflammation was recognised, but there existed no knowledge of adhesions as an entity.

CHAPTER III.

THE LITERATURE AND HISTORY OF ADHESIONS.

In 1942 Floyd Boys wrote a most comprehensive review of the literature and history of adhesions. He says that adhesions have been known for one hundred and fifty years and the pathology has been understood for fifty years.

Payr (1914) did original work on adhesions, using Iron and Magnet as a treatment. In this paper Payr demonstrated how a gastrointestinal tract, filled with a suspension of reduced iron, would rise up in peak in responce to the attraction of the magnet. The loops could be inspected with Roentgen. He attempted to break up artificially produced adhesions by the force of the magnet, and showed that scrupulous macroscopic study afterwards failed to show injury to the intestine from this procedure. Not even a trace of capillary haemorrhage could be found in the intestines where they had been drawn up and long held up against the abdominal wall.

In a woman who showed signs of adhesions in the sigmoid flexure, an enema of iron suspension was given. Here application of the magnet caused distinct local pain.

His improved magnet had a force of about 75 kgm. The Roentgen Ray could examine the intestine when pulled in any direction. He used this procedure in the reduction of torsion of intestines and in enteroptosis.

He fed rabbits and guineapigs on the iron suspension and found that their health was not affected in the least by adding this to their diet.

Payr (1914) recognised that three and a half per cent of all major operations are performed for the relief of intestinal obstruction, and Christopher (1939) wrote that thirty to forty per cent of these were due to peritoneal adhesions.

Duff (1939) by pneumoperitoneum examined one hundred and

forty eight cases who had previous laparotomies, and found that eighty to ninety per cent had evidence of adhesions.

Boys (1942) emphasizes the importance of the prophylaxis of adhesions, and says that the most serious considerations are the facts that:

(a) Some individuals have an apparent tendency to develop adhesions as compared to others.

(b) The notorious tendency for adhesions to reform after operative treatment to remove them, and that they often reform in greater numbers than before.

Lehman (1940) found the formation of adhesions in the peritoneum of patients who present keloidal abdominal scars, and it is a question here whether these patients have a "fibroblastic diathesis."

Historic Review of the Literature.

Gay (1935) and his co-workers gave a review on the medical progress of abdominal adhesions.

1350—1750. Establishment of the Symptomatology of Adhesions.

Abdominal maladies were long ago considered to be due to some ailment of the peritoneal lining or "Sacred Sac." Some people believed that abdominal disease was associated with disfavour of the Diety, others that it was a Demoniac possession.

Hypocrates and Galen believed that all abdominal complaints were accounted for by the faulty mixtures of the four "humours" [1]) (Boys 1942).

By the time of the Renaissance (1450—1650), physicians could already differentiate between the three "belly passions" and called them "renal passions", "iliac passions" for peritonitis and "colic passions" for obstruction. (Boys 1942.)

---

[1]) It was believed that health depended on four humours or fluids. The fluids were blood, phlegm, yellow bile and black bile. These fluids were responsible for the four humours or temperaments namely: Sanguine, phlegmatic, choleric and melancholy respectively.

1750—1800. The Relating of Symptoms to Structural Changes.

The establishment of a Medical School at Bologna in 1260, was associated with the commencement of regular examinations by postmortem.

Morgagni in 1761 wrote his "De Sedibus et Causis Morborum." He published the first account of lesions of the body in his five volumes, of which translations are still available at many libraries.

In his first Volume Morgagni describes an acute abdomen and a gangrenous peritonitis found on post-mortem examination. He was assisted by his able colleague Valsalva, to whom he frequently refers. He describes the pain, vomiting, course of the disease and post-mortem appearances of many fatal cases who died of acute conditions.

The first medical men to establish adhesions as a true entity, were John Hunter 1728—1793, a London surgeon and anatomist (who has been mentioned in the previous chapter), Bichat 1771—1802, who was a Parisian physician extra-ordinary, and Rene Laennec 1781—1826, surgeon and anatomist at the time of the French Revolution.

Hunter concerned himself most with adhesions, and ascribed them to peritonitis. He called the sticky substance exudated from the bowel "gluten."

1800—1870. The Establishment of Peritoneal Adhesions as a true disease entity.

Peritonitis during this period was established as a true cause of adhesions in the abdomen, and the causes of peritonitis were recorded, e. g. Appendicitis, Puerperal fever, subphrenic abscess, perforations, ectopic pregnancies, cholecystitis, et cetera. Physicians still knew nothing about the histology or bacteriology of peritonitis.

1870—1900. Establishment of the Causes of Peritonitis.

Knowledge improved concurrently with the advances in bacteriology and surgery. As a result the causes of adhesions were later classified under four main groups. Traumatic, Bacterial, Thermal and chemical. The alleviation of adhesions by surgical methods was first practiced in the early and middle 1800's.

1900—1940. The Causes and Prevention of Adhesions.

(i) *Limitation of injury to the peritoneum.*

Rough handling of the peritoneum should be avoided such as: vigorous use of retractors, careless use of packing swabs, especially using them dry — which would remove the mesothelium.
Unnecessary sponging, failure to peritonealize denuded surfaces, unnecessary large sutures and unnecessarily long cut ends would be aggravating factors.
Haemostasis is important, and Halsted's (1925) principles of absolute haemostasis were stressed. Reichert, Gerbose and Halford (1939) favoured the use of electrocautery, and said that a small eschar is formed in this way, which ceases exudation from the peritoneal surface.

In the prevention of adhesions the following were observed:

(a) *The avoidance of Bacterical Infection:*

Absolute aseptic technique should be practised in abdominal operations. (Hunter was the first surgeon to recognise adhesive inflamation of the peritoneum.)

(b) *Strong chemicals,* such as disinfectants, should be avoided in the peritoneum.

(c) *Thermal Injury* to the peritoneum is possible when hot solutions are used, and indiscriminate use of the cautery should be avoided.

(d) *Foreign Bodies,* particularly if bulky, can produce death (accidental) but the chief one with which we are concerned is material used for drainage. The other common one employed is *Talc Powder* (for gloves) which is now known as a cause of peritoneal adhesions. (Boys 1942.)

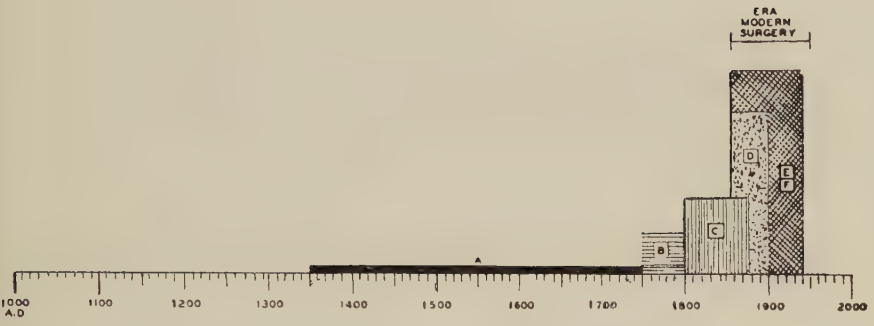
(ii) *The Inhibition of fibroblastic tissue surfaces.*

Fibrolysin and iodides have been tried without success and were demonstrated by the pioneers in this field. (Payr 1922.)

(iii) *The keeping apart of peritoneal surfaces.*

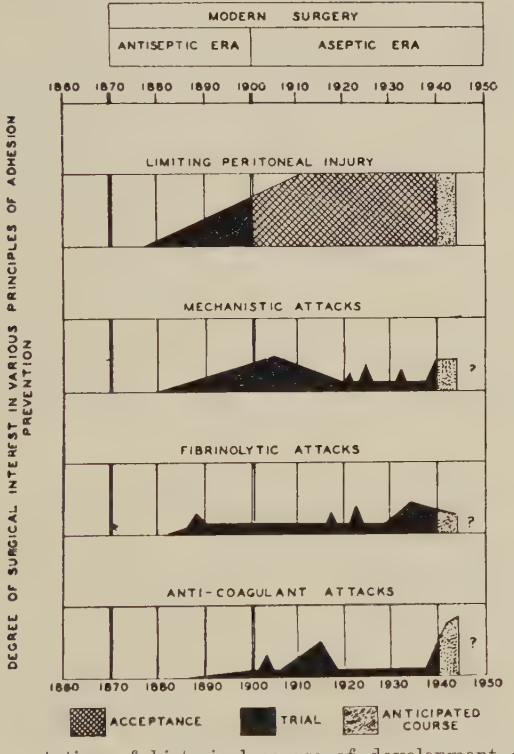
Membranes absorbable and non-absorbable were used unsuccessfully. Rubber, metal and others were tried.
Recently Johnson (1937) reported successful amployment of human amniotic membrane in preventing adhesions in the abdomen, and around nerves and tendons. In guineapigs adhesions were prevented in this way by experiment.

Davis and Aries (1937) used beef alantoic membrane and found it superior to human amniotic membrane.
Chao, Humphreys and Penfield (1946) successfully used autoclaved human amniotic membrane, and called it amnioplastin.
Lubricants have been tried unsuccessfully. Amongst others: comphorated oil, fat, agar, gum arabic, gelatin, paraffin, vaselin, and colloidion have been tried. They have all been abandoned. (Boys 1942.)
Further extensive methods were employed in attempts to find the answer. Baum (1894) used cloth made of woven catgut, fish bladder and the peritoneum of a young calf soon after slaughtering. These were applied to raw areas with fair results.
Morris employed sterilized oxen peritoneum (Gargile membrane), which experimentally he found unsatisfactory. (Ochsner and Garside 1932.)
Sterile olive oil was tried by many surgeons, but Pope (1914) and others found that it irritated the peritoneum.
Camphorated oil, Lanolin, sterile omental oil, and humanol have been tried but oils proved very disappointing on experimental investigation. (Ochsner and Garside 1932.)
Other substances which have been tried include: gelatin and gum acacia, mucin, peptonized milk, egg albumin, and vitreous humour of calves eyes, but were found useless.
Normal saline, citrate solution, magnesium sulphate solutions, iodide in syrup of hydrochloric acid, fibrolysin, and hypertonic sodium chloride solution were employed without success. (Ochsner and Garside 1932.)



Historical development of knowledge of adhesions through Gay's six periods. A. Adhesion symptomatology established (1350-1750). B. Adhesion symptomatology related to structural changes (1750-1800). C. Structural changes related to disturbed function (1800-1870). D. Causative agents of peritonitis established (1860-1900). E. Relief of adhesions (1870 to present). F. Prophylaxis of adhesions (1860 to present).

Photocopy by kind permission Floyd Boys (1942) Surg. II p. 118.



Schematic representation of historical course of development of methods of adhesion prevention.

Photocopy by kind permission Floyd Boys (1942) Surg. II p. 118.

(iv) *The Production of increased fluids in the abdominal cavity.*
Fluids to keep apart the surfaces of the peritoneum have been tried — both hypotonic and hypertonic, saline and glucose.

Ochsner and Garside (1932) presented experiments with normal saline solution in the dog against both the formation and reformation of adhesions. Of their control animals 100 % formed adhesions, and of the treated animals 85 % formed adhesions.

(v) *Mechanical Methods. Pneumoperitoneum* was used in 1908 by *Bainbridge* with clinical but not experimental success.
Hertzler (1919) advised that gentleness during operation should be kept in mind. No foreign bodies should be inserted into the peritoneum, and denuded areas of serosa should be covered.
Increased Movements of the bowel during and after operation by manual replacement during operation, distention of the large bowel immediately after operation by bulky enemas and post-operative bed positions were tried, but all these attempts were unsuccessful.

(vi) *Prevention of Coagulation of the exudate.*

To understand the prevention of coagulation, it is necessary to summarise briefly the pathology of the formation of adhesions.
The chronological development of the formation of fibrous adhesions take place as described by Richardson (1911) and Coudry (1934).

(a) There is an initial injury or death of the surface endothelium.

(b) An exudate is poured out at the site of trauma.

(c) The exudate coagulates and fibrin is formed.

(d) If adjacent traumatized surfaces are adhered by the fibrin, the result is fibrous tissue invasion and a fibrous adhesion is formed.

(e) This ultimately terminates in a contracted scar.

We see therefore that unless the fibrin is removed or the injured serosal surfaces are kept apart by some means until healing has occurred, organisation will proceed over the fibrin scaffolding, resulting eventually in a fibrotic peritoneal adhesion.

In the chemical attack on fibrin, "fibrolysin" which the Pharmacopoeia describes as liquor thiosimamide with Sodium Salicylate, and which was claimed by Hebra and Unna (1892) to absorb both fibrin and scar tissue was later injected by Muller (1929). It was found to have no therapeutic effect in animals

Foreign Digestive Ferments.

The use of digestive ferments was investigated by several scientists. Stewart (1918) described an experiment which could convince one that the action of pepsin results in the absorption or digestion of fibrin.

In 1922 Payr used Pepsin-pregl solution. Pepsin as a digestant and pregl (an iodide solution) added to sterilise the ferment.

Ochsner and Garside (1932) stated that this substance in experiments was found to inhibit the formation of adhesions.

Kubota (1922) at a later date than Payr, was unable to confirm this finding, and used Papain as the digestant or enzyme of choice and obtained satisfactory results.

Using papain in solutions ranging from one in one hundred thousand to one in four hundred thousand, Ochsner and Mason (1928) found papain effective as treatment to some extent, but was later discarded as ineffective in a suitable series of experiments by Ochsner and Garside (1932).

Amniotic Fluid. Summarizing the work done by Trusler (1931), Wagensteen (1933) and Johnson (1927), one can say that the theoretical basis for the use of amniotic fluid as treatment is indefinite. The experimental work does not convince us of great success.

In preventing Coagulation of the exudate, Heparin, sodium citrate in two per cent solution, Hirudin and Peptone have been used. Of these the most useful seems to have been Heparin used by Lehman and Boys (1940).

While the results are encouraging in animals, the possibility of intra-peritoneal haemorrhage in the human being represents a serious disadvantage.

From this review it seems as if heparin was the most promising drug, but more work has been done by others since then. The more modern work will be described later.

CHAPTER IV.

THE PERITONEUM.

The Peritoneum is the sturcture which is our primary focus in the study of adhesions. For this reason a detailed account of its development, anatomy and physiology with their applied relations are given below. The sensitivity of the peritoneum is also described.

The Development of the Peritoneum
(from Hamilton, Boyd and Mossman. 1952).

The development of the peritoneum must be followed from the time when the *Intra Embryonic Coelom* appears, of which the pericardial cavity is the midline portion. This pericardial cavity lies at first, anterior to the bucco-pharyngeal membrane, but later ventral and caudal to the membrane.

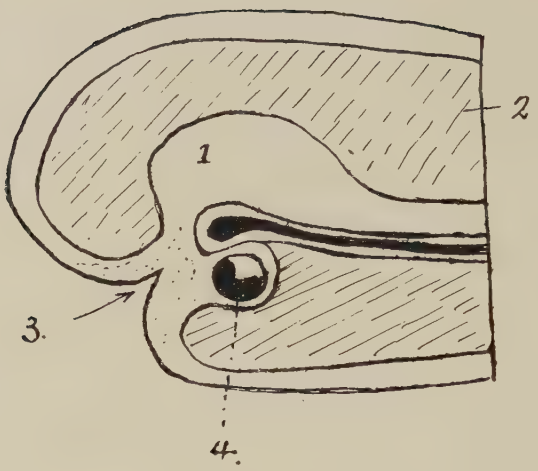
The early heart tube invaginates the part which lies ventral to the foregut. The visceral layer of mesoderm which covers the heart tube is continuous dorsally with the mesocardium and this mesocardium is attached to the mesoderm of the foregut on its ventral surface.

In the early stages the lateral and ventral wall of the pericardium is in contact with ectoderm.

When the pleural cavities expand and the chest wall is established in the third month, the pericardium becomes buried within the thorax.

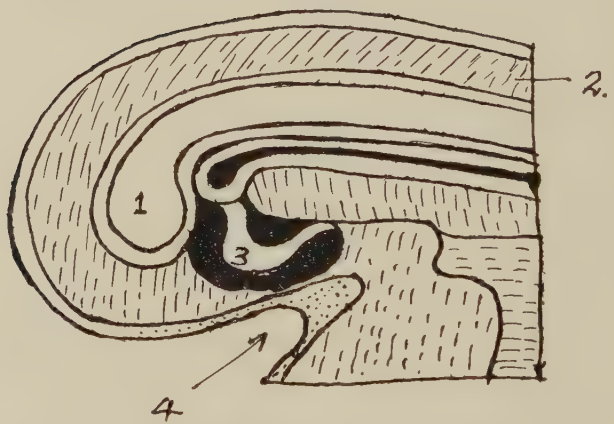
If the costal cartilages, muscles and sternum fail to differentiate in this area, the heart remains herniated through the chest wall. (Ectopia cordis.)

At the 10-somite stage degeneration of the mesocardium begins, and later it disappears allowing the heart tube to lie free in its pericardial cavity. At the entrance (venous end) and exit (arterial



1. Brain plate.
2. Amniotic cavity.
3. Septum transversum.
4. Primitive heart.

Human Embryo 7 Somite stage.



1. Forebrain.
2. Amniotic cavity.
3. Heart tube.
4. Septum transversum.

Human Embryo 20 Somite stage.

Drawings inaccurately sketched from Textbook of Hamilton Boyd and Mossman. (1946).

end) the mesocardium persists. Here the parietal pericardium and visceral pericardium are continuous and are called the somato- and splanchnopleuric layer respectively.

The pericardial cavity is large at this stage and communicates with the peritoneal cavity by the pleuro-peritoneal canals.

When the lung buds appear, the visceral layer of mesoderm covering them is invaginated and forms the *pericardio-peritoneal canal* which may now be called the primitive pleural cavity.

As the lung buds develop, the heart slowly descends in its relation to other structures. At the 6 mm stage the lung is increasing in size and at the same time a primitive pleural cavity extends into the body wall.

The pleuro-peritoneal membrane now appears which is attached to the body wall laterally, and extends between the primitive pleural and the peritoneal cavities.

From the 15 mm stage, enlargement of the pleural cavity takes place cranially. With this enlargement of the pleural cavity, the posterior attachment of the pleuro-peritoneal membrane is pushed downwards (caudally) until finally the posterior attachment is at a lower level than the anterior attachment.

The liver increases in size, and muscular tissue extends into the membrane. The result is that the pleuro-peritoneal communications are reduced in size. By the time the embryo reaches the 20 mm stage, these communications become obliterated. Occasionally the fusion of the membrane does not occur, especially on the left side and a congenital opening persists. This opening between pleural and peritoneal cavities will allow abdominal viscera to herniate through the diaphragm (hiatus hernia).

The Peritoneal Cavity and Diaphragm.

After closure of the communications between pleural and peritoneal cavities, the diaphragm consists of:

(a) The central portion which represents the original septum transversum. It becomes the central tendon.

(b) The dorsal portions or the pleuro-peritoneal membranes. (Their anterior margins are continuous with the central tendinous portion.)

(c) A dorsal portion derived from the mesentery of the oesophagus.

(d) Portions from the circumference on each side which are gradually added to the peripheral part of the pleuro-peritoneal membrane as the lungs expand.

The Lesser Sac.

At the 4 mm stage, and before the stomach has commenced rotation, small excavations or *pneumato-enteric recesses* appear, on the left and right of the dorsal mesogastrium. The left one disappears, but the one on the right gradually extends posterior to the stomach, and upwards to the right of the oesophagus, behind the right lobe of the developing liver and towards the right lung bud.

Eventually this recess forms a large cavity which has a small opening into the peritoneal cavity.

As the dorsal portion of the diaphragm develops and the pleuro-peritoneal canals are closed, the caudal portion of the pneumato-enteric recess is separated to form *the primitive lesser sac.* Later this sac undergoes changes related to the changes in the position of the stomach. With the rotation of the stomach and associated duodenum, the lesser sac cavity comes to lie to the left and dorsal to the stomach. The dorsal mesentery of the stomach elongates and its gastric attachment is carried to the left.

The ventral mesentery of the stomach undergoes a similar change during rotation, so that its free edge lies to the right, and this mesentery forms the lesser omentum.

The free edge contains the bile duct, and forms the anterior boundary of the aditus to the lesser sac, the Foramen of Winslow.

Futher changes undergone by the lesser sac are:

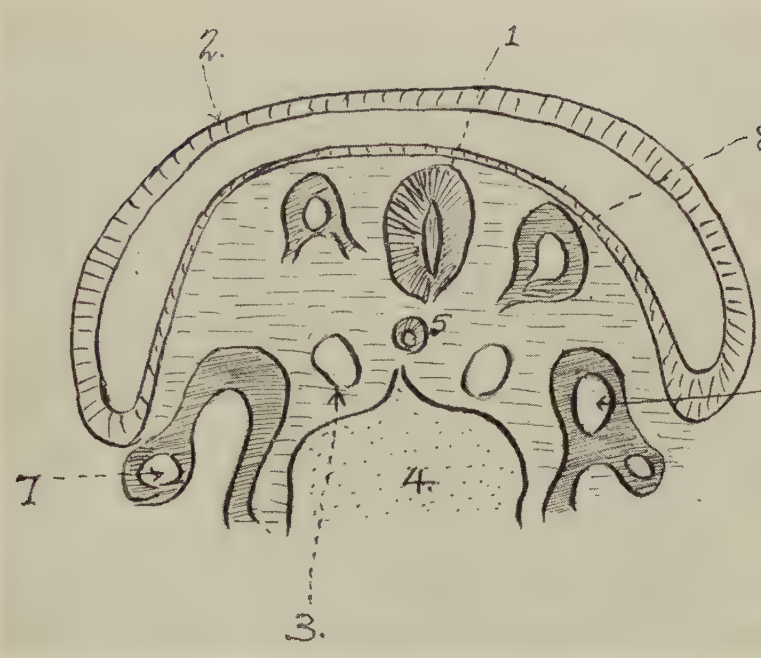
(a) The development and growth of the spleen.

(b) The fusion of the proximal part of the dorsal mesogastrium to the posterior abdominal wall.

The Great Omentum.

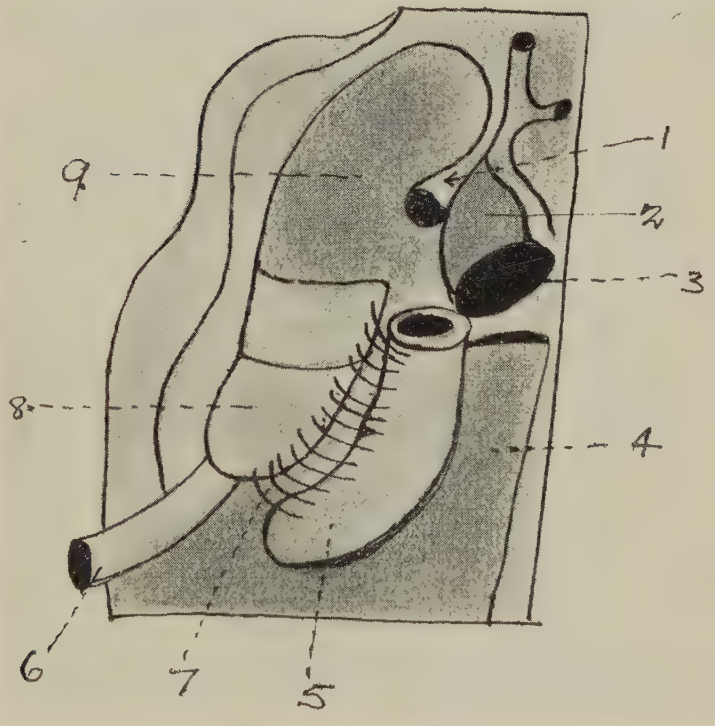
At the 50 mm stage, the lesser sac is enlarged by downward growth of the dorsal mesogastrium — particularly that part which lies below the spleen and gastro-splenic ligament. This portion

1. Neural tube.
2. Amnion.
3. Rt. Dorsal Aorta.
4. Yolk sac cavity.
5. Notochord.
6. Intra Embryonic Coelom.
7. Rt. Umbilical vein.
8. Somite.



Human Embryo 14 Somite stage.

1. Duct of Cuvier.
2. Rt. Pleural cavity.
3. Rt. Pleuro-peritoneal canal.
4. Peritoneal cavity.
5. Stomach.
6. Left umbilical vein.
7. Gastro hepatic omentum.
8. Rt lobe of liver.
9. Pericardium.



Diagramatic illustration.

Drawings inaccurately sketched from Textbook of Hamilton Boyd and Mossman. (1946).

forms an apron-like fold of mesentery, the greater omentum. It is attached to the greater curvature of the stomach and to the posterior abdominal wall above the attachment of the transverse mesocolon. By further growth of its caudal folded edge the greater omentum extends anterior to, and then distal to the transverse colon.

The posterior layer of the omentum subsequently fuses with the peritoneum of the posterior abdominal wall, from below upwards. It also fuses between its attachment and the root of the transverse mesocolon, with the antero-superior surface of the transverse mesocolon itself, and with the transverse colon. As a result the greater omentum is eventually attached to the anterior surface of the transverse colon.

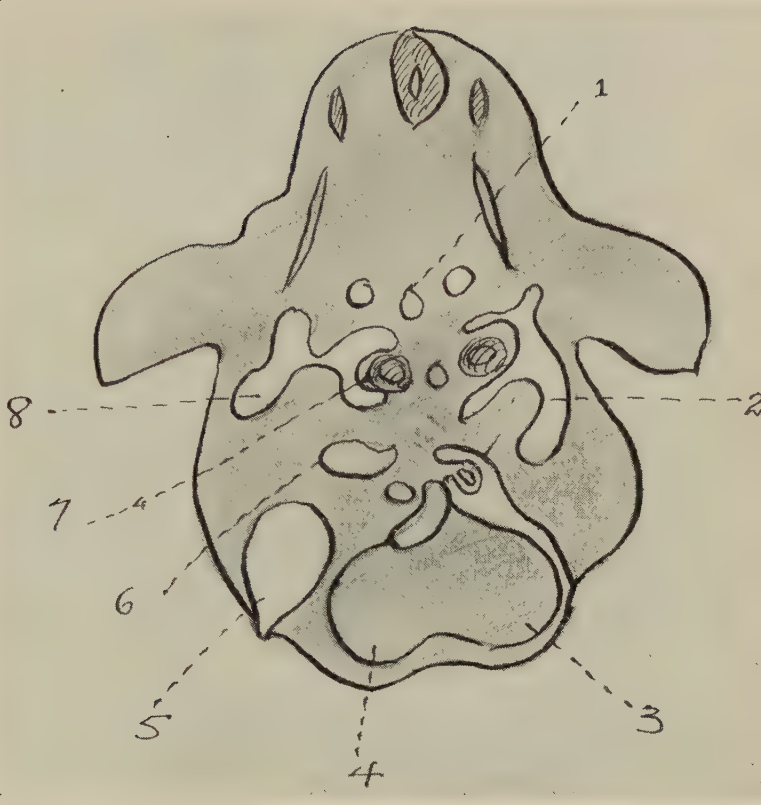
There are many abnormal folds of the peritoneum which might be mistaken for adhesions by someone unacquainted with the attachments of peritoneum in unusual situations. For its understanding, it is necessary to describe briefly:

The Early development of the Digestive tube.

The earliest observations are made in embryos at the third or fourth week. (Hertzler 1935.) The first evidence of the stomach and gut with the beginning mesentery is seen at six weeks. The migration of the caecum can also be noted in this stage microscopically. The caecum goes over the primitive digestive tube from left ot right to lie below the stomach. The duodenum pushes beneath the mesenteric root and so becomes retro-peritoneal. At the same time the colon slides across the duodenum and becomes attached to the lateral abdominal wall on the right.

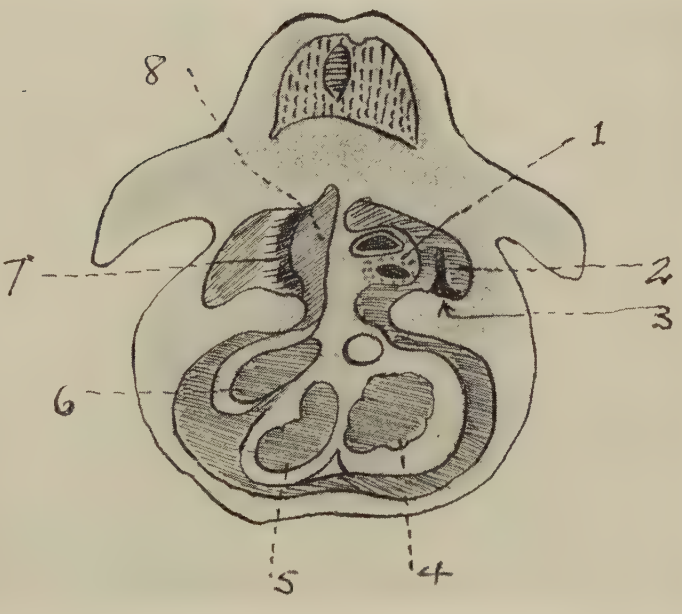
It is of great importance where this future colon becomes attached. It might be attached considerably higher than the normal site. If the attachment is high, the transverse colon may form a loop producing the double-barrel colon. In such cases the peritoneum joining this loop of colon, is part of the duodenocolic ligament. If the attachment of the colon takes place near the ileo caecal valve peritoneal folds may extend over the colon and caecum, and the great omentum may be attached to the colon permanently. These abnormal attachments may be mistaken for adhesions.

1. Dorsal Aorta.
2. Left pleuro-peritoneal canal.
3. Lt. ventricle.
4. Rt. ventricle.
5. Rt. atrium.
6. Inf. vena cava.
7. Rt. Lung bud.
8. Peritoneal cavity.



Section of 8 mm. Human Embryo.

1. Left lung bud.
2. Pleural cavity.
3. Pleuro-peritoneal membrane.
4. Left ventricle.
5. Rt. ventricle.
6. Atrium.
7. Pleuro-peritoneal membrane.
8. Pleuro-peritoneal canal.



Section at 10 mm. stage.

Drawings inaccurately sketched from Textbook of Hamilton, Boyd and Mossman. (1946).

Part of the great omentum may become separated and attached to the lateral abdominal wall, extending from the duodenum.

The unusual folds are mostly found in the hepatic or caecal region, and function may be normal in spite of their existence.

The hepato-duodenal ligament or fold is found extending from liver to duodenum. It forms the roof of the foramen of Winslow and encloses the common bile duct and hepatic ducts.

The Cysto-duodenal ligament extends from the gall bladder to the duodenum.

A variety of folds occur lateral to the gall bladder. They extend from liver to colon. They are called hepatico-colic ligaments and are easily mistaken for adhesions, especially if inflammation occurs in this neighbourhood.

Anomalies of the Omentum.

These depend on the time of attachment of the omentum to the colon, and they occur during development, especially during rotation.

The omentum may be attached to the parietal wall as well as to the ascending colon. (Ligament of Haller.) This condition closely resembles adhesions. (Hertzler 1935.)

The omentum may also be attached to the ascending colon and the abdominal wall. When attached near the caecum it may form a thickened pad of fat. It may extend across the gut and form a thickened mesentery which may be attacked by the surgeon when seen during an operation. More frequently the omentum extends to the hepatic angle and continues down the ascending colon. On occasions it may cover the whole of the ascending colon. A fold may extend from the lesser omentum to the hepato-duodenal ligament, and is confusing during inflammation in this area. A small fold is but rarely seen extending downwards from the lesser omentum, called the third omentum.

Omentum extending over the colon is sometimes simulated by persistence of the foetal state of the descending colon. In these cases the colon is almost entirely extraperitoneal.

Further the omentum may be seen attached to the liver, and completely covering the gall bladder.

Many unusual folds are found about the appendix.

Summary of Pleural and Peritoneal Development.

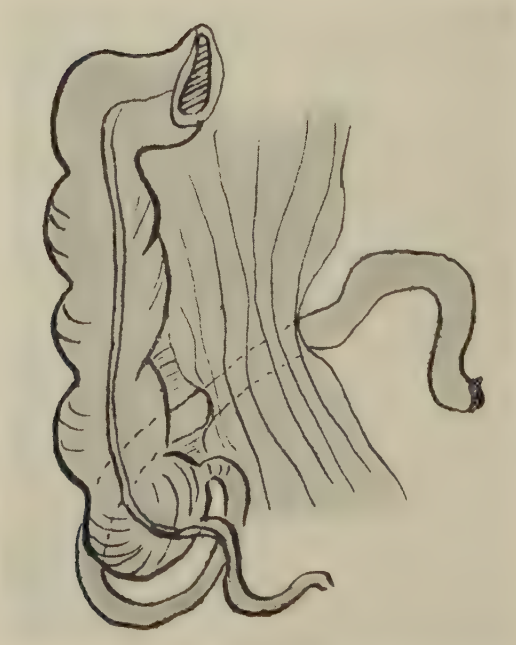
An Original Imaginary Drawing.

1. Amniotic cavity.
2. Forebrain.
3. Heart tube.
4. Pericardial cavity.
5. Lung buds.
6. Pleural cavity.
7. (between 5 and 6). The Pericardio-pleural canal.
8. Pleuro-peritoneal membrane (part of primitive dorsal portion of diaphragm).
9. Septum transversum which becomes the central tendon of the diaphragm.
10. Liver.
11. (Below 8). A Pleuro-peritoneal communication.
12. Foramen of Winslow and lesser sac above it.
13. Primitive stomach undergoing rotation.
14. Greater sac.
15. Yolk sac.

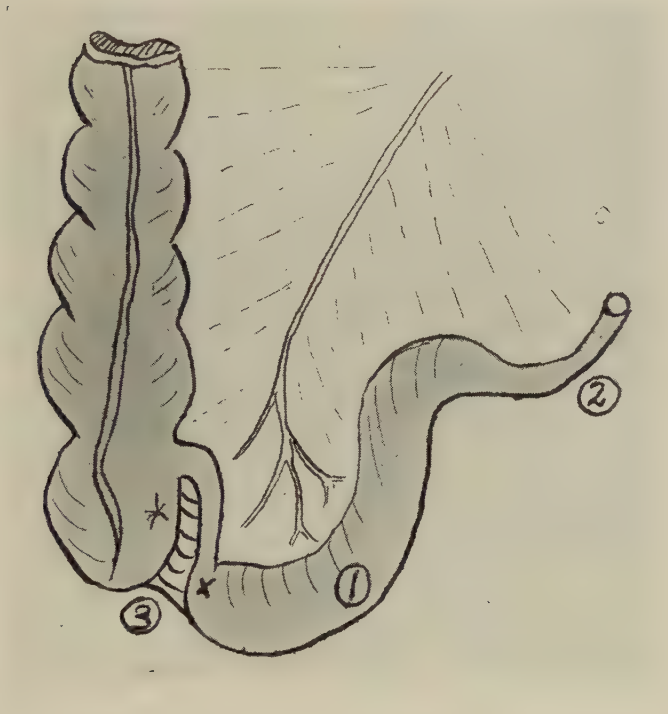
Inaccurate Sketches from Hertzler (1935).

1. Hepatico-colic Ligament.
2. Cysto-duodenal Ligament.
3. Hepata-duodenal Ligament.
4. Stomach.

Retrocaecal position of terminal Ileum.



Original Diagram of what may be called the Inferior inter-ileocaecal Mesentery.



X. Site at which obstruction occurs due to kinking.
1. Hypertrophied Ileum.
2. Normal Ileum.
3. The Inferior inter-ileocaecaal mesentery.

(The Appendix has been removed and the abnormal mesentery overlooked at a previous operation.)

The Bloodless fold of Treves or ileocaecal fold, sometimes contains blood vessels.

The mesoappendix may lie behind the caecum, and this is not uncommon. The appendix may be entirely retroperitoneal, and the terminal ileum may be anchored sharply downwards.

The terminal lieum may be retro-caecal in position, and here a part of the ileum is also retro-peritoneal, becomes free, retro-caecal again behind the caecum and free at its termination. (See illustration.) Such an ileum may become oedematous during acute inflammation and cause acute obstruction.

Original observation can account for four cases of an unnamed membrane in the ileo-caecal region. An accessory mesentery binding the caecum to the terminal ileum. (The inferior inter-ileocaecal mesentery.) In all four cases the terminal ileum was obviously hypertrophied proximal to this abnormal mesentery. Three of the four cases were seen durng operation for appendicitis. The fourth was re-operated twelve months after appendectomy and was diagnosed as adhesions.

In all cases symptoms were identical to those of appendicitis, and in one of them the appendix was normal on inspection. Kinking and hypertrophy were the prominent features seen in all cases.

Accessory Peritoneal Bands.

These are of interest as they may give rise to kinking or obstruction, and should be distinguished from adhesions.

Different theories have been postulated on their causation.

Arbuthnot Lane held that bands were due to the result of the assumption of the erect posture, and that these bands are ligaments to hold the gut upward, and prevent sagging.

Lee McGregor (1940) says that this view is not generally accepted.

McGregor (1940) considers the inflammation theory, held by Jackson and others, to be unlikely, as the bands are:

(a) Too constant in situation.

(b) Constant in their normal bloodsupply unlike inflammatory tissue.

He writes that the *Congenital Theory* is the most widely accepted.

The bands are frequently present at birth, and are most likely to arise during development and gut rotation. During migration of gut primitive mesenteries tend to disappear and secondary ones develop. Failure in the normality of these processes may result in accessory membranes. These membranes are found at birth, but even so, may never cause symptoms, or cause trouble only in adult life.

McGregor (1940) describes six of these peritoneal bands.

(1) *Lane's Ileal Membrane* which is a thickened portion of parietal peritoneum found in the terminal two or three inches of terminal ileum, drawing it downwards to the right iliac fossa. Obstruction may occur, but in many cases seen, there is no hypertrophy of the ileum above this membrane.

(2) *The Mesosigmoid Band.* This membrane is found at the junction of the iliac and pelvic colons, and holds down this junction to the pelvic brim. Arbuthnot Lane called it the "first and last klink". He regarded it as the first to appear evolutionary, and last because it is lowermost in the intestinal tract. He held that it frequently causes partial obstruction.

(3) *The Mesocolico-jejunal membrane.* This band varies in length and extends from the transverse mesocolon to the proximal part of the jejunum.

(4) *The intercolic membranes.* These are peritoneal membranes found at the two colic flexures. They draw together:

(a) The ascending colon and proximal part of the transverse colon at the hepatic flexure.

(b) The distal part of the transverse colon to the descending colon at the splenic flexure (Payr's membrane). These membranes can cause the well known double-barrelled colon, and may cause obstruction.

(5) *Jackson's Membrane* is a fold of parietal peritoneum which extends over the caecum. Its origin is the abdominal wall laterally, and it ends in the anterior longitudinal band of the caecum, or in the visceral peritoneum of the terminal ileum and appendix. It varies in breadth and position of

origin and is usually very thin. Its bloodvessels are also thin and run parallel to the band.

(6) *The Cystogastrocolic Band.* This is a fold which extends from the gall-bladder to the duodenum and great omentum or to the transverse colon. The cysto-duodenal ligament described above by Hertzler (1935) is probably part of this band. According to McGregor (1940) this band may produce symptoms of partial obstruction to the outlet from the stomach, and this may occur soon after birth.

The Gross Anatomy of the Peritoneum.

The peritoneum is a serous membrane which is highly absorptive and lines the abdominal and pelvic cavities as the parietal layer. It also covers the viscera contained by the cavities as the visceral layer. In the male the peritoneal cavity is a closed sac. In the female it communicates with the uterus and vagina through the fallopian tubes. Infections can therefore reach the peritoneum via the vagina, uterus and tubes as is found in gonococcal peritonitis or in puerperal sepsis. In life the peritoneum is movable on the extraperitoneal fat and can be stretched without tearing. This is a great advantage in surgery.

The lesser omentum is formed by two layers of peritoneum, but the greater omentum is formed by four layers. The posterior two layers of the greater omentum enclose the transverse colon and then run backwards and upwards to form the transverse mesocolon.

The lesser sac lies behind the stomach and is a diverticulum of the great sac, communicating by an opening the Epiploic Foramen of Winslow.

The *Greater Omentum* is a protective sheet which covers the viscera below the level of the stomach. It is often the first structure visible when the peritoneum is opened, and it contains a variable amount of fat. Apart from its origin, the omentum is free in its left and right and also the lower margin, so that it can easily be mobilized in abdominal operations. The greater omentum is attracted by inflammatory processes to any region in the abdomen. It surrounds the area of inflammation, adhesions

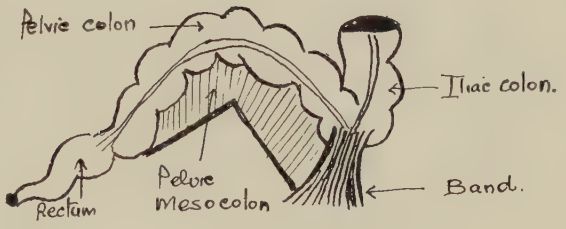
Figures 1 to 5 are inaccurate sketches from Lee McGregor (1940).
No 6 is original.

I

1. Lane's ileal membrane.

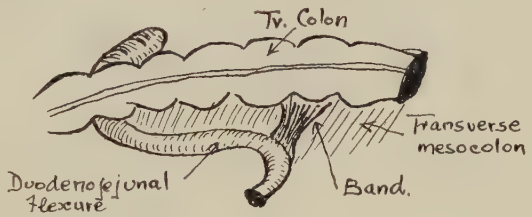
II

2. The mesosigmoid membrane.



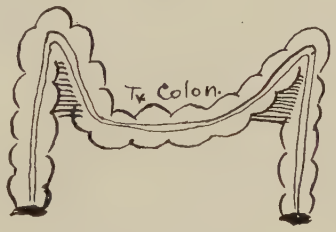
III

3. The mesocolicojejunal membrane.



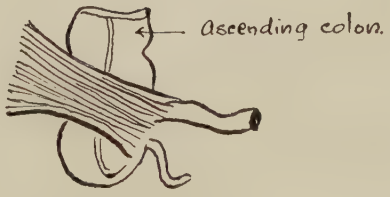
IV

4. Intercolic membranes (Payr).



V

5. Jackson's membrane.



VI

6. The crystogastrocolic Band.

are formed and thus the spread of infection is limited. For this reason it has been termed the abdominal policeman.

The Lesser Omentum extends from the lesser curvature of the stomach and the first part of the duodenum to the porta hepatis. It is formed by two layers of peritoneum, which are closely applied. It is a thin sheet, excepting at its right border where the two layers are separated by the Hepatic artery, portal vein and bile duct. The two layers are continuous with each other at this right free border. On occasions the lesser omentum extends beyond the free border and may then be attached to gall-bladder, along the duodenum, or even to the transverse colon.

The lesser sac extends upwards between liver and diaphragm. Below its boundary is the transverse colon. Anteriorly it is related to the liver, lesser omentum and stomach and the anterior two layers of the greater omentum. Its posterior wall is formed by transverse colon, transverse mesocolon, pancreas, left kidney and diaphragm.

Herniation of intestine through the epiploic foramen may occur causing strangulation. To free this strangulation the omental bursa may have to be aspirated, or it may be necessary to mobilize the duodenum. (Bruce and Walmsley 1939.)

Peritoneal spaces which are easily infected.

(1) The lesser sac (omental bursa).

(2) Subphrenic spaces.

(a) *Right.*

i. Anterior Intra-peritoneal.
ii. Posterior Intra-peritoneal. (pouch of Morison).
iii. Extra-peritoneal Space.

(b) *Left side.*

i. Anterior Intra-peritoneal.
ii. Posterior Intra-peritoneal. (upper part of the omental bursa).
iii. Extra-peritoneal Space.

(3) The pouch of Douglas.

(4) The Iliac fossae.

Diagrams No II to VI inaccurately sketched from Lee Mc Gregor (1940).

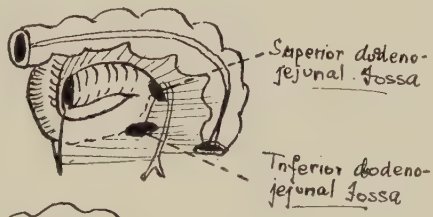
Drawing No 1: Original.

I

I. Foramen Epiploicum (Winslow).

II

II. The Paraduodenal Fossa.

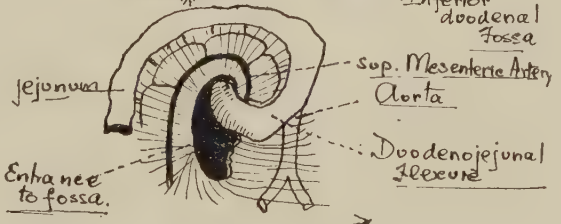


III

III. The Superior and Inferior Duodenojejunal Fossa.

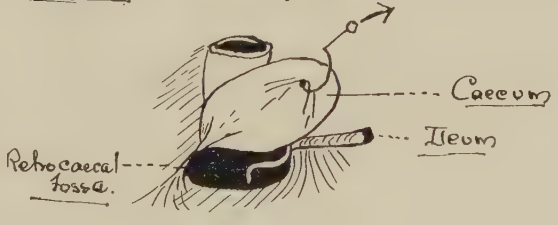
IV

IV. The Inferior Duodenal Fossa.



V

V. The Mesenterico-parietal Fossa of Waldeyer.



VI

VI. The retrocaecal Fossa.

(5) The paracolic gutters.

(a) The Right paracolic gutter communicates with the pelvis below and the recess of Morison above.

(b) The Left paracolic gutter opens into the pelvis below and above its upper extremity, is separated from the spleen and the lienorenal recess by the phrenicocolic ligament — a fold of peritoneum which passes laterally from the left colic flexure to the diaphragm.

The Peritoneal Fossae are of great surgical importance as sites of internal herniae. They are:

(1) *The Lesser Sac* which has already been described.

(2) *The Duodenal Fossae* which are illustrated below.

(3) *The Caecal Fossae* which consist of the

(a) Ileocaecal.
(b) Ileocolic, and
(c) Subcaecal.

(4) *The Fossa Intersigmoidea* which is situated at the apex of the V-shaped insertion of the pelvic mesocolon.

CHAPTER V.

THE PHYSIOLOGY OF THE PERITONEUM.

"A detailed knowlegde of the physiology of the peritoneum belongs to the surgeon's necessary preparatory studies." (Hertzler 1935.)

The surgeon is interested mostly in the rate of absorption and site of absorption from the peritoneum. The factors which may hasten or delay absorption are also of importance.

The normal physiology of the peritoneum.
(Hertzler 1935.)

The avenues of absorption are possibly twofold, namely the lymph vessels and the bloodstream. *The Lymph Theory.* It was once thought that stomata existed between the lymphatics and peritoneal surfaces. By special stains and sections these have been proved to be artefacts. Although mediastinal and retro-peritoneal glands transport malignant cells by way of their lymphatics, they do not do so by way of the thoracic duct. So experiments in which cannulae are inserted into the thoracic duct would not always find the correct route of lymphatic transport.

Hertzler (1935) states that the lymphatics are the chief avenues of removal of solid particles probably with the aid of phagocytic cells.

The Blood Vessels. These are probably the most important in absorption if we take into account the laws of osmosis. In experiments certain dyes appear in the urine earlier than they do in the lymphatics.

Rate of absorption from the Peritoneum.

The rate of absorption depends upon the concentration and type of fluid injected. With hypotonic solutions it is found that absorption is rapid until osmosis is balanced when it becomes slower.

Absorption of isotonic solutions continues at the same rate for several half hour periods.

Temperature does not seem to effect the rate, but increased osmotic pressure of the blood hastens absorption. Adrenaline is found to increase the osmotic pressure of the blood.

Hertzler's own studies on absorption were done by injecting given quantities of fluid into a series of animals of the same litter. The animals were killed at half hour intervals. He found that the percentage of absorption was decreased if the amount injected was excessive.

If the amount injected does not exceed ten per cent of the body weight, thirty per cent is absorbed in the first half-hour. After two hours less than thirty percent will remain. Absorption is delayed if the pressure of the fluid is higher than diastolic blood pressure. Hertzler stresses the importance of this, pointing out nature's delay in absorption in pathological conditions. In his experiments individual variations were astonishing.

The Site of Absorption.

For a long time the diaphragm was thought to be the chief area of absorption, and tilting the patient was thought to be of value. All these ideas were fallacies. Physiologically the peritoneum has the same structure throughout and throughout its area absorption proceeds with equal rapidity.

The Absorption of solid particles.

Hertzler's research included many substances on many species of animals.

Lampblack, carmine and silver chloride were chiefly used, and the animals used were rabbits and guinea pigs, but also dogs and mice. The same deductions were made in all the experiments despite the variation in species. He injected sodium chloride intraperitoneally followed by a silver nitrate solution. He found that the peritoneal vessels became constricted but dilated after a few minutes, causing peritoneal exudation. Simultaneous with the exudation there occured a sweeping of particles to the nooks and dependent portions of the peritoneal cavity and around the

greater omentum. This process was as marked at the diaphragm as in the pelvis.

The greatest accumulation seemed to be around the great omentum and the mesenteric root.

The visceral peritoneum of the intestinal surface remained almost free from particles. This was found constant whether the omentum was intact or removed prior to the experiment.

After localization of the particles they are surrounded by exudate and the process of encapsulating a foreign body proceeds. Encapsulation by fibrinous exudate requires two or three hours. Fibrin replaces the fibrinous exudate in a few days and seals off the foreign body.

Some granules are carried to the anterior sternal lymph gland, as it has been shown by many writers, but other glands also receive them.

Nacent silver chloride particles seem to pass directly into the bloodstream as they are soon seen in the glomerulus of the kidney. Only a few are found in the mediastinal glands (Hertzler 1935). Cell numbers increase in the peritoneal fluid after encapulation by fibrin. The cells escape from the peritoneal surfaces where they are irritated by the foreign substance.

During encapsulation many particles are taken up by cells. The predominating cells are polymorphs at first but later mononuclears.

The cells that are laden with particles enter the lymphatic vessels and become permanently secured in some of the lymph glands. Particles are found in lymph glands but also in lymph vessels and Hertzler says that this proves that they travel in the same way as cancer cells.

Factors Hastening Absorption.

About this little is known. If intra-abdominal pressure is increased it will hasten absorption, provided the pressure is not enough to retard venous return. Other factors which hasten absorption are those which result in a decrease in blood volume. Severe haemorrhage, witholding fluid intake and severe acute diarrhoea will all cause a decrease in blood volume, and thus absorption will be hastened under these circumstances.

Factors Delaying Absorption.

This subject has not been given much attention and study, but is of importance to the surgeon. According to Hertzler, it has been long known that glycerine and glucose lessen absorption. In concentrated solution they produce an exudate.

Opuim lessens the rate of absorption by decreasing peristalsis, but rate of absorption is not depesdent on rate of peristalsis.

Glycerine and formalin were used and found to produce uniform results. Many other substances were tried. Glycerine delays absorption for a time. If solutions stronger than ten per cent are used exudation occurred. All strengths of solutions were finally absorbed.

Injections of two per cent formalin prevented absorption for twelve hours to several days. In the same species the time of absorption varied. The drug produced albuminous exudate on peritoneal surfaces.

Absorption was delayed when ascitic fluid or cyst fluid was added to saline solutions and injected intraperitoneally. Absorption ultimately occurred.

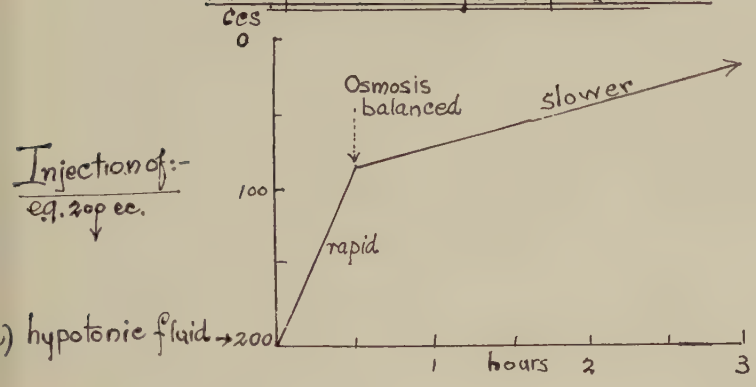
Exudation of albumin is readily demonstrable with a half per cent solution of formalin. If a five per cent solution is injected into the peritoneal cavity, the albumin exudated is sufficient to undergo spontaneous coagulation when allowed to cool.

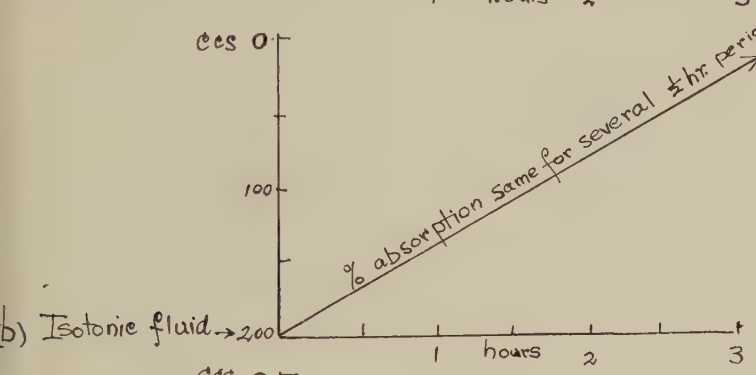
Absorption of Blood from the Peritoneum.

To do this the peritoneum must absorb an isotonic fluid and also eliminate solid particles.

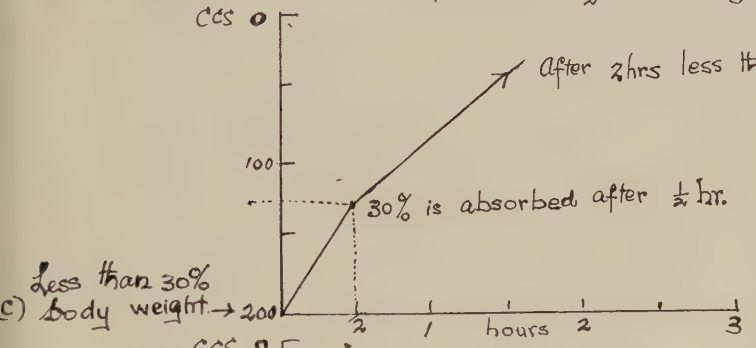
Blood which has been defibrinated is absorbed completely in four to ten hours. Auto blood is absorbed with equal rapidity. If blood in the peritoneum coagulates, the fibrin causes an exudate in the peritoneum as well as into the perivascular tissues. As soon as the serum is separated from the clot, absorption begins. The clot may take days to decrease in size. These changes can be studied in injury to the viscera. For a clot to absorb completely, weeks or months may be required. The solid material is probably eliminated by phagocytosis, but it is possible that by exudation the solid particles may be liquefied and absorbed without cellular reaction.

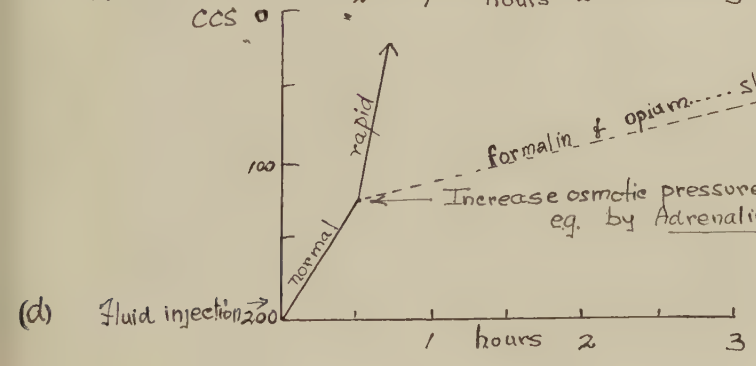
Absorption rate from peritoneum. Graphic Summary





Deductions from Hertzler (1935).





Hertzler thinks that the important fact is that if blood is left in the peritoneal cavity, one should prevent its contact with denuded peritoneal surfaces.

The Effects of Inflammation on the Absorption Rate.

The effect on absorption depends on the type and stage of the inflammation.

When there is excessive fibrinous exudate in the peritoneum the rate of absorption is considerably delayed. One can understand this, because the result of irritation to the peritoneum is exudation and not absorption.

One can say that inflammation inhibits absorption, but it produces substances in the perivascular tissues which give rise to symptoms of peritonitis when they are absorbed.

The Effect of Decreased Peristalsis on Absorption.

The Fowler position was once adopted to cause drainage into the pelvis — where peristalsis would be less encountered and where it was thought that absorption would be slower. We know now that the absorption rate is the same from all areas of the peritoneum.

Opuim is the only drug which lessens the peristalsis and so lessens absorption.

The Effect of increased Intra-abdominal Pressure on Absorption.

If the pressure is slightly increased, it will hasten absorption. Should pressure be increased sufficiently to disturb the circulation, the rate of absorption is considerably decreased.

Nature limits the rate of absorption by producing various degrees of distension, and by diminishing peristalsis. (Hertzler 1935.)

The Sensitivity of the Peritoneum.

The *parietal peritoneum* receives its sensation from the tissues which cover it. In other words from the cerebro-spinal nerves, and pain occurs when the parietal peritoneum is irritated. It is sensitive to stimuli effecting mixed nerves. The parietal peritoneum has an accurate localizing sense, as is demonstrated under local anaesthesia. Light touch causes no sensation but clamping

or pulling is felt as pressure which corresponds to deep muscle sense. When irritated by a needle, acute pain is felt, and the patient can localize the site of irritation. It is insensitive to a single prick owing to the large meshes of the plexus. The needle may penetrate without striking a nerve. (Hertzler 1935.)

The Visceral Peritoneum experiences pain when the intestine is distended. Through the tissues of the intestinal wall and the plexuses of Meisner and Auerbach the sensitivity is derived.

The visceral peritoneum is supplied with the two systems of plexuses belonging to the sympathetic system. Sympathetic nerves contain no medullated fibres on careful microscopic investigation.

Although some writers assume that sympathetic nerves cannot transmit pain, pain is experienced in the viscera. Thus we must accept that pain is transmitted through sympathetic fibres. (Hertzler 1935.)

In their textbook, Bruce and Walmsley (1939) state that from an affected viscus, afferent impulses go to the central nervous system and so set up a viscero-sensory reflex.

Both peritoneum and intestinal wall are insensitive to mechanical injury. Gut can be pinched and crushed without causing pain. If it is pulled (without traction on the mesentery) there is no pain. The gut may be sutured without pain, but cutting may or may not cause pain. (Hertzler 1935.)

Stretching the plexuses within the intestine, or pulling on the nerve trunks will cause severe pain. In the area of the appendix, stretching causes epigastric pain, and dislodging a gallstone under local anaesthesia results in pain and vomiting. Traction on mesentery causes pain and vomiting. (Hertzler 1935.)

The Inflamed Peritoneum.

Both parietal and visceral peritoneum become much more sensitive during inflammation.

Both become sensitive to touch and this occurs with the beginning of exudation. When the fibrin state is approached the peritoneum becomes less sensitive.

The Physiology of the Great Omentum.

The function of the omentum is protective, but it is not vital and may be completely removed. Occasionally it is congenitally

absent. During inflammation its power to move can be studied. It has absorptive power, and this can be studied by suspending it in a strichnine solution. Convulsions will take place. From the omentum absorption rate is slower than from other peritoneal surfaces.

Insoluble particles inserted into the general peritoneal cavity are usually surrounded by the omentum. (Hertzler 1935.)

The Sensitivity of the Omentum.

It has not been shown to contain nerves, and is not sensitive to manipulations. Resection and ligation cause no pain. When inflamed it is always adherent to some other surface of peritoneum, and pain here may originate from the parietal or visceral nerve supply to which it has become attached.

The *Active mobility of the omentum* and the way this takes place will be described below under its applied physiology.

The Applied Physiology of Intraperitoneal Adhesions.

In 1944 Bernard Steinberg gave an account of his studies of the applied physiology of intraperitoneal adhesions, and the processes of their formation.

Richardson (1911) found that within ten minutes after the serosa is injured there occurred a pouring out of serum and fibrin over the denuded surface.

The injured surface attracts an adjoining loop of bowel covered with normal serosa, or omentum, or parietal peritoneum. The two surfaces in contact are agglutinated by fibrin in approximately two hours. (Hertzler 1921.)

In eighteen hours the adhered surfaces are already firmly attached by the fibrinous bands. (Heinz 1901.)

Proliferation of fibroblasts occurs after the third day in obvious numbers, and this process may continue until the fibrin has been completely replaced by connective tissue. (Hertzler 1921.)

These adhesions which are formed are efforts of the body to protect its tissues by repairing and circumscribing the injured surfaces.

The body often removes adhesions after the process of repair by means of digestive ferments. Some observers believe that

removal of adhesions can only take place prior to fibrosis, but there is strong evidence that fibrous bands may be obliterated by digestion or other processes. (Hertzler 1921.)

Due to intestinal peristalsis these bands may be stretched and thinned out, and ultimately disrupted. The anastomoses of lymph and blood vessels have been established between two surfaces through the adhesions as early as eighteen to forty eight hours after the formation of adhesions.

Gundermann (1913), Silvester (1911), Simer (1934), Simer (1937), Hertzler (1921) state that adhesions may develop through the media of the following:

A. *External influences which injure the endothelium.*
As mentioned above in Chapter 3.

B. *The Inherent Tendency* on the part of the body to produce fibrous tissue. This can occur beyond the body's need.

The Omentum. The ability of the *omentum* to attach itself to injured peritoneal areas in various parts of the cavity has been investigated. It has been suggested that *the omentum possesses* active mobility. (Cornie and Carnot 1898.)

The omentum contains no muscle tissue, so on anatomical grounds it would be unable to move. The fact that it is directed particularly to the injured area of serous membrane would not be explained.

Rubin (1911) thought that the movements of the omentum were due to intestinal peristalsis, intra-abdominal pressure, and the static condition of the stomach and colon.

Cantacuzene (1923 and 1931) explained the movements of the omentum on electrical grounds. His explanation was supported experimentally, and he proved that the difference of electric potential existing between the omentum and normal abdominal contents is eight or less millivolts. Two poles of a circuit are established after injury. The omentum is electro-negative under normal conditions. If an area of peritoneum is injured the omentum becomes electro-positive and is attracted to the injured surface which becomes electro-negative.

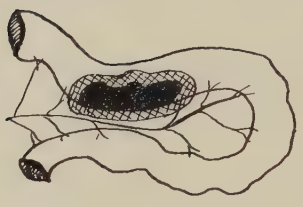
At the point of contact the fibrinous exudate which is present already, or appears shortly thereafter, glues the surfaces together.

Original Diagramatic representation of Adhesions.

a.

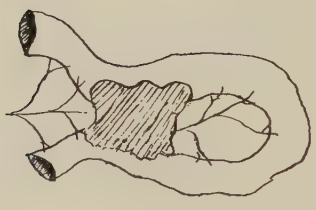
Trauma tð Peritoneum.

b.



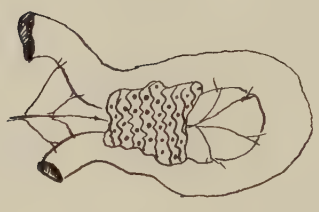
In 10 minutes Serum and fibrin exudate.

c



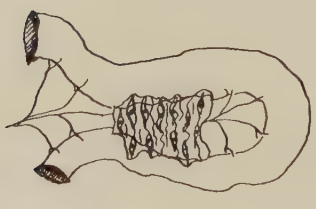
In 2 hours agglutination by fibrin to some adjoining surface.

d.



In 18 hours fibrinous bands and leucocytes found. In 18—24 hours new blood and lymph vessels.

e.



3rd—5th day proliferation of fibroblasts.

f.

In 10 days firm fibrous tissue.
In 4—5 weeks scar tissue.

Investigators also showed that peritoneum which has been immunized has an electro-positive charge which diminishes the electro-potential between injured and normal surfaces. They found that certain dyes and bacteria have an action similar to the immunized peritoneum. Hertzler (1921) suggested that these observations should lead to methods for preventing the formation of adhesions.

CHAPTER VI.

THE DIAGNOSIS OF INTESTINAL OBSTRUCTION.

The most frequent result of adhesions is intestinal obstruction, particularly of the small intestine. For this reason it is necessary to give an account of the diagnosis of intestinal obstruction.

For the "*Recognition of Intestinal Obstruction*" we are indebted to Wagensteen's (1942) account.

He writes that in every reported series, where mortality is considered, the importance of an early diagnosis is emphasized. Frequently it is stated that diagnosis is difficult in bowel obstruction because the physical findings are meager.

Wagensteen (1942) states that four questions should be considered in the diagnosis.

A. *Is the Bowel obstructed?*

The patient complains of three things: Pain, vomiting and distension. The diminished power of the gut to contract when the lumen is blocked causes intermittent pain of a crampy nature. The onset is sudden, increases quickly to become a severe pain, and this intensity persists for one to three minutes. The pain diminishes and disappears as suddenly as it began. There are free intervals which vary in duration, but the pain recurs repeatedly. In strangulating obstructions, fluid and blood is transudated into the peritoneal cavity, and in these cases the pain is more continuous, and the abdomen becomes tender to palpation. When pain and noise or borborygmus occur at the same time, this painful contraction is established as intestinal colic. The first necessary step is to decide whether intestinal colic is present or absent.

Vomiting. In obstruction the vomiting becomes frequent and abundant. The explanation is that the intestinal block brings stagnant contents from lower to higher levels in the alimentary

canal. If such contents accumulate in the stomach, copious vomiting occurs. In cases where there is excessive distension without vomiting, the obstruction is invariably in the large intestine. The distention is then situated in the flanks.

Faeculent vomiting is invariably a condition which is due to small intestine obstruction. The distension is then in the centre of the abdomen.

If a duodenal tube is passed when the colon is obstructed, the fluid recovered presents gastric or biliary features.

The fluid aspirated in small intestine obstruction is greater in volume which shows that there is gastric retention. The aspirated fluid is yellowish-brown and has a faecal odour typical of the contents of the lower ileum.

The Physical Findings are usually of little help in the diagnosis. The general appearance of the patient suggests a potentially serious ailment. Usually the respiration and blood pressure are normal. The temperature and pulse are usually slightly raised. The patient may not appear to be very ill apart from the pain, vomiting and distension.

Late in obstruction the patient becomes dehydrated and more changes in the bodily economy occur. The patient has an anxious expression, the features are sunken, the pulse is feeble, and the extremities are cold and livid.

Laboratory Investigations do not help to determine the diagnosis. Severe vomiting is followed by haemo-concentration; haemoblobin, red cells and leucocytes are increased. (Wagensteen 1942.)

In high intestinal obstruction Demidova (1940) observed the following data:

	Normal
Red cells six million	(4.5 to 5.5 million)
Haemoglobin 120 %	(85 % Sahli.)
and Leucocyte count 30.000	(4000—8000) with a tendency to appearance of premature cells.

In low intestinal obstructions Demidova (1940) found changes which deviated less from the normal findings.

The urine is usually scanty in obstruction, and albumin or casts may be found.

There is no impairment of kidney function. If vomiting con-

tinues for 48 hours the non-protein nitrogen is increased. The blood chlorides are decreased, and there is increase in the CO_2 combining power of the blood.

(Normal values are:
Non-protein Nitrogen: ..... 25—35 mg %
Chloride (as Nacl.): ..... 450—500 mg %
CO_2 combining power: ..... 53—72 c. c. s. CO_2 per 100 cc blood.)

X-ray Observations. With the help of X-ray films one can obtain reliable information on the degree, extent and site of the distended segments of bowel.

Normally, gas is present throughout the alimentary canal. Under normal conditions it can be seen on X-ray films of the adult abdomen only in the stomach and colon. These are the sites where food and contents of the intestine remain for some time. In the small intestine gas is not seen on the roentgen film. Although gas is present throughout the small intestine, there is an intimate mixture between it and fluid on account of the rapid passage. This makes the gas invisible on X-ray examination. (Wagensteen 1942.)

Should stasis occur, however, gas and fluid separate out, and gas becomes visible. It does not matter whether the stasis is due to a paralytic (inhibitive) or mechanical cause. In the normal infant and child, gas is seen in the small intestine on X-ray films. This variation remains until the child reaches the age of three years. (Wagensteen 1940).

If the small intestine of a dog is obstructed experimentally, gas is seen regularly on roentgen films after four to five hours.

Visible gas in distended loops of small intestine in the adult signifies stasis in the intestine. Stethoscopic examination helps to distinguish between mechanical and paralytic (inhibitive) stasis. (Wagensteen 1942.)

The second question we must ask is:

B. *Where is the Obstruction?*

In acute obstruction of the large intestine the distension is usually limited to the colon. If the distension extends to the small intestine as well, one of the lips of the ileo-caecal valve is

deficient. In the small intestine gas is characterised by its central location. The shadow shows a transverse long axis.

In considerable dilatation, two adjacent loops may be seen separated by their thinned out, narrow walls. Should an X-ray show a fairly thick wall intervening between two loops, it suggests exudate or fluid between them.

The shadows of gas in an obstructed small intestine give a stepladder appearance to the coils. The mucosal folds within the bowel lend a feathery appearance. Acute angulations are described as "hairpin turns". Valvulae conniventes are more frequent in the jejunum than in the ileum. In the ileum, therefore, the shadows are characterless as compared with the feathery appearance of the jejunum when distended.

Difficulty arises in distinguishing borderline cases when it is a question whether colon or jejunum is distended. If doubt exists a barium enema should be given. (Wagensteen 1942.)

The competency of the ileo-caecal valve is important in distension of the colon. If the lower lip of the ileo-caecal valve is deficent, gas could regurgitate into the ileum.

Distension, neusea and vomiting with faeculent regurgitation, and the presence of intestinal colic indicate obstruction of the small intestine. Gross distension without nausea or vomiting, and where no intestinal fluid is obtainable on aspiration of the stomach is synonymous with obstruction of the colon.

X-rays are of value in revealing the exact location of the distended segments.

If distension is limited to the colon and intestinal colic is present, the site of obstruction is in the colon. (Wagensteen 1942.)

C. *Is the Obstruction Incomplete or Complete?*

The extent to which the coils are distended gives us a fair idea as to the completeness of the obstruction. The distension of complete obstruction in the large intestine is accompanied by alarming distension of the colon and the caecum.

If obstruction in the colon is incomplete the distention is less and gas is passed per rectum.

In the small intestine complete or incomplete obstruction is determined after an evacuant enema has been given. It must then be observed whether gas persists on the roentgen film.

The chief source of gas in the intestine is air that has been swallowed. Enemas will remove gas which is present distal to the obstruction as the bowel in this area retains its normal function.

Gross distension of the small intestine without visible gas in the colon indicates complete obstruction. If there is distension of the small intestine but gas persists in the colon, the obstruction is incomplete.

D. *How is the Bowel Obstructed?*

It is obstructed in two ways:

(a) Simple obstruction by interfering with the continuity of the lumen of the bowel.

(b) Strangulating obstruction which not only blocks the intestine, but interferes with its blood supply.

In simple obstructions there is no tenderness, but if the blood supply is interferred with, blood and serum escape into the peritoneal cavity which causes tenderness.

Burgess (1929), writes: "If obstruction can be located to the large intestine there is a 91 % chance of its being of a malignant nature — that is roughly a 9—1 chance. On the other hand, if the large intestine can be excluded as the site of obstruction, then the odds are nearly 300 to 1 against malignancy. (Out of 586 cases of small intestine obstruction only two were due to malignant growth); 88 % of small intestine obstructions are due to adhesions or internal strangulations."

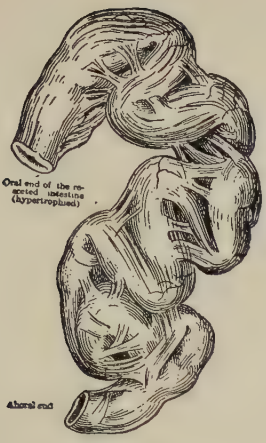


Fig. 662.

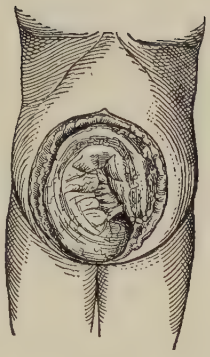


Fig. 663.

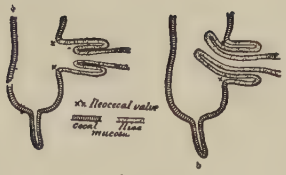


Fig. 664.

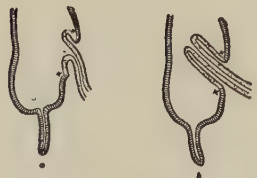


Fig. 665.

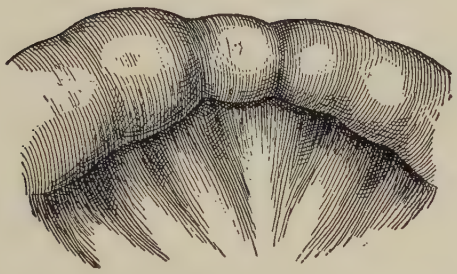


Fig. 666

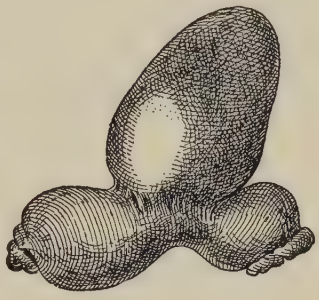


Fig. 667.

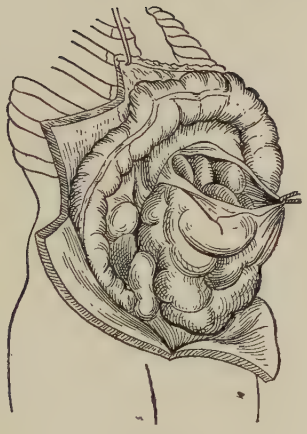


Fig. 668.

Fig. 669.

Figs. 662—669. — Forms of intestinal obstruction.

Fig. 662. — Stenosed ulcerated tumor of the pylorus; coils of intestine agglutinated by numerous adhesions. Resected intestinal coils (Payr).

Fig. 663. — Volvulus of the sigmoid flexure (Richardson's case).

Fig. 664. — a, Invaginatio iliaca; b, invaginatio ilia-ileocolica (H. Lorenz).

Fig. 665. — a, Prolapsus ilei; b, invaginatio ileocolica (H. Lorenz).

Fig. 666. — Obstruction of the jejunum due to gall-stone, showing the contraction of the muscular fibers of the intestine upon the stone, which is smaller in diameter than the lumen of the gut (Mixter's case).

Fig. 667. — Meckel's diverticulum (Bunts).

Fig. 668. — Hernia into the fossa duodenojejunalis (after Cooper).

Fig. 669. — Strangulation by a band (Warren Museum).

From da Costa's "Modern Surgery". Ed. 10, 1931.

By kind permission of The Editor, W. B. Saunders Co, Philadelphia.

Dr da Costa is now deceased.

CHAPTER VII.

THE HISTOLOGICAL GENESIS AND FREQUENCY OF ADHESIONS.

The work done and the opinions expressed on the causation and prevention of abdominal adhesions from the earliest times up to the beginning of the last decade have already been described. Modern work and views on this subject will now be described.

Extensive work on adhesions was accomplished by Krook in 1947.

In the histological genesis of an adhesion, he states, it is necessary to have an exudate and the formation of a fibrinous adhesion. This may be retrograde, but may develop into one which is more permanent. As we have seen in previous work, surface cells of the serosa must be injured for exudate to form. An uninjured layer of surface cells of the peritoneum is able to prevent formation of adhesions, but only if the tissue underlying the serosa is normal. (Ladwig, 1928.)

Thus, according to Ladwig if the underlying tissue is changed, for example by an action from within the lumen of the intestine, adhesions can still form even if the surface cells of the intestinal wall are intact.

The length of time required for adhesions to form has been stated above. Thus fibrinous fibres are present after ten minutes, fibrinous adhesions after two hours, and transformation into fibrous adhesions begins from the third to the fifth day. Firm connective tissue is found after ten days and cicatricial tussue after four to five weeks. (Hertzler 1923.)

Ladwig (1928) stated that he found muscle fibres in adhesions in their border portions, but they were most probably drawn out mechanically from the wall of the bowel into the adhesion. He stated that he was unable to demonstrate nerve fibres in adhesions

as was stated by Wereschinski (1924). As long as the adhesions are in the fibrinous stage, it is not only possible that a regression can take place, but it is quite a common occurrence. The fibrin is dissolved by a fermentive chemical process. The ferment originates from both living and disintegrating leucocytes. Peristaltic action loosens the adhesions and so resorption of fibrin residues are facilitated. The last phase is the renewal of the peritoneal coating.

In a fibrous adhesion retrogression is not so common but still possible. Microscopic specimens are described were cavities and degenerated areas were found; the oldest were fifteen years. Ladwig (1928).

Ocsner and Garside (1932) give us a slightly different description of the histological process, and add some useful information on the repair of the serosa after adhesions have undergone retrogression.

According to them an inflammatory process follows after trauma to the peritoneum and the adhesions which follow on the trauma are usually temporary, as they become absorbed after the inflammatory process has subsided.

They think that the proteolytic enzyme is liberated from polymorpho-nuclear leucocytes as they are destroyed. The inflammatory reaction occurs almost immediately after injury of the serosa, and a layer of fibrin covers the involved surface. This fibrinous exudate may cover uninjured endothelium as well as the traumatized area. In the earliest stages of the inflammatory reaction there is an effusion of serum which contains large numbers of phagocytic neutrophils.

If there is no infection mononuclear leucocytes on the surface become flattened, and finally actually cover the denuded area. The most interesting fact is that by this process endothelialization progresses over the whole peritoneal defect at once, and does not extend from the periphery towards the centre as in the case of the skin. (Ochsner & Garside 1932.)

The neutrophilic leucocytes produce a strong proteolytic ferment which was called leucoprotease by Opie (1910) who regarded it as being like trypsin.

Senn (1888) proved that firm adhesions formed in six to twelve hours.

Hertzler (1921) showed that fibrous tissue formed in three to

five days and that this tissue could be digested by pancreatin. Similarly embryonic fibrous tissue could be digested by pancreatin.

Digestion of adhesions, according to Hertzler, is impossible after adult fibrous tissue has been laid down.

In 1928 Ladwig's work showed that old adhesions can still undergo retrogression, and his work is mentioned above.

Payr (1914) helps us to classify adhesions as follows

1. Fibrinous adhesions.
2. Fibrous adhesions.
   (a) Temporary and
   (b) permanent, which may further be subdivided into:
      (i) Those rich in connective tissue, poor in blood vessels, and are further characterised by the fact that their causal processes have healed; so regression is not likely after reduction.
      (ii) Those which are rich in blood vessels and vital; these adhesions show a tendency to progression, possibly because of some persisting inflammatory process.

After these adhesions are reduced there is a strong tendency to regression.

The Frequency of Adhesions.

The methods by which we can investigate patients for the frequency of adhesions according to Krook (1947) are:

1. *X-ray examination with pneumoperitoneum.*
   X-ray alone will only help us to report a small number of adhesions. Pneumoperitoneum will only show viscero-parietal adhesions. The adhesions which are inter-visceral remain invisible in this type of examination which is not free from danger.
2. *Operation.* At operation it is difficult to register completely the total number of adhesions, as incisions are limited in size. With ordinary incisions e. g. for gall bladder or appendicitis the accessibility to the peritoneal cavity is deficient.

In the writer's opinion it is self evident that in treatment of adhesions, a large midline laparotomy is required.

3. *Obduction.* (Post mortem examination.)
According to Krook (1947) obduction is the most satisfactory method of registering adhesions. By this method they can be recorded to their fullest extent. Examinations of this type are of a specialised nature, and up to the present they have not yet been used in statistical investigations for the frequency of adhesions.

Ochsner and Garside (1932) write that Flesch Thebesius reports one case in which twenty three operations were necessarily performed because of the repeated formation of adhesions.

Payr (1913) reports that in a series of three thousand abdominal operations, ninety eight cases, or 3.26 per cent, were subjected to subsequent operations due to reformation of adhesions. In addition sixty five cases required laparotomies due to peritoneal adhesions. These cases did not have previous operations.

Burgess (1929) published statistics collected from Mr. H. S. Souttar's report on acute intestinal obstruction. His table illustrates combined statistics from seven hospitals.

The total number of cases considered was 3064. In these cases both small and large intestine obstructions, due to any cause, were taken into account. Of the 3064 cases, 342 obstructions were due to adhesions, and the percentage mortality was 31.

In his paper on obstruction Burgess (1929) states that out of 586 cases of small intestine obstruction be found that 88 % were due to adhesions and internal strangulation.

TABLE ILLUSTRATING Mr. H. S. SOUTTAR'S REPORT ON ACUTE INTESTINAL OBSTRUCTION. COMBINED STATISTICS FROM SEVEN HOSPITALS.

(A. H. Burgess in Lancet, April 27, 1929)

Cause.	Age decade.								Site.				Duration in days.					Operation.					Result.		Totals.	Mortality (per cent).
	1	2	3	4	5	6	7	8	Small intestine.	Right colon.	Left colon	Rectum.	½	1	2	4	+	Reduction.	Enterotomy	Enterostomy.	Anostomosis.	Resection.	Lived.	Died		
Gall-stones	...	..	..	..	1	7	15	5	26	...	2	....	...	...	3	10	12	...	25	3	..	..	14	14	28	50
Carcinoma	...	2	7	31	52	114	110	41	2	46	246	54	1	12	51	46	121	...	..	313	48	37	202	156	358	43.5
Adhesions	29	72	65	52	49	29	27	15	308	23	10	2	9	67	88	61	59	283	..	..	36	20	235	10	342	31
Internal strangulation	17	42	34	31	25	27	25	11	211	6	6	....	13	38	50	28	17	134	..	27	32	33	149	74	223	36
Intussusception (idiopathic)	577	14	7	9	5	2	...	..	526	100	14	....	130	173	91	37	24	544	2	13	48	58	476	137	613	22
Intussusception with tumour	8	3	..	1	2	2	1	..	15	...	2	.....	...	2	3	1	4	13	4	2	2	9	11	6	17	35
Volvulus	2	6	11	10	12	18	11	4	39	18	20	....	3	10	12	11	9	47	3	17	12	18	36	38	74	51
Total (excluding hernias)	...	..	..	..	...	...	...	..	...	...	...	...	...	...	..	..	...	...	..	...	..	..	1123	532	1655	32.
Inguinal hernia	31	33	37	54	82	17	104	65	457	31	13	Om. 29	70	101	74	44	41	501	2	11	27	34	451	83	534	16
Femoral hernia	2	3	27	83	157	148	175	97	537	5	4	29	128	127	99	66	82	618	1	14	55	57	557	118	675	20
Umbilical hernia	...	..	5	4	28	76	68	19	159	36		12	8	23	30	29	35	170	1	14	27	33	129	71	200	35
Total hernias	...	..	..	..	...	...	...	..	...	.....		....	...	..	..	...	...	...	..	...	..	..	1137	272	1409	19.3
Grand total	..	..	..	..	...	...	...	..	...	.....		....	...	..	..	...	...	..	...	..	..	..	2260	804	3064	26.2

Om = Omental.

	Cases.	Deaths.	Mortality (per cent).
Mortality (excluding hernia and idiopathic intussusception)	1042	395	37.9
Mortality of hernia and intussusception combined	2022	409	20.22

By kind permission of The Editor, The Lancet. Prof. A. H. Burgess is now deceased.

TABLE 1.

Frequency of adhesions after different laparotomies observed at relaparatomies or examinations with pneumoperitoneum.

Year	Author	Laparotomy for	No. of cases	Freq. of adhesions	Method of exam.	Comments
1922	Naegeli	Surg. disease	165	78	Pneumoperit.	Op. for adh. incl.
1929	Clairmont	„ „	290	90	Relaparotomy	Op. for adh. and scar hernia incl.
„	„	„ „	107	82	„	Op. for adh. and scar hernia not incl.
1929	Ranzi	„ „	111	67	„	Only relap. for new dis. incl.
1935	Kaufman	„ „	509	88	„	Op. for obstr., adh., scar hernia incl.
1921	Naegeli	„ „ (major laparot.)	114	91	Pneumoperit.	Op. for adh. incl.
1929	Clairmont	Ventr. + bile-tract disease	—	87	Relaparotomy	Op. for adh. and scar hernia incl.
„	„	Diff. intestinal dis.	—	70	„	
1921	Naegeli	Surg. disease (minor laparot.)	34	41	Pneumoperit.	Op. for adh. incl.
1929	Clairmont	Appendicitis (pos. susp.)	—	75	Relaparotomy	Op. for adh. and scar hernia incl.
1941	Burger	See preceding	—	49	„	Very small % adh. discomfort incl.
1922	Mayer	Gyn. disease	—	87	Relaparotomy	
„	„	„ „	23	65	„	1 st op. at own clinic
1923	Haug + Heudorfer	„ „	236	91	„	
„	Haug + Heudorfer	„ „	96	83	„	1 st op. at own clinic
1933	Turunen	„ „	184	87	„	Op. for adh. and scar hernia incl. No essential diff. whether 1st op. at own or other clinic.
1941	Burger	„ „	—	73	„	Very small % adh. discomfort incl.
1903	Essen-Möller	Pregnancy (caesarean op.)	76	90	Caesarean op.	76 pat. reop. 101 times. Collection from literature.
1922	Martius	See preceding	33	42	„	22 sect. prof. with 27 % adh.
1923	Krause	„ „	36	67	„	5 of these op. 2 or more times.
1930	Hasselblatt	„ „	57	61	„	50 sect. prof. with 60 % adh.
1941	Burger	„ „	51	63	Relaparotomy	

By kind permission of Dr. S. S. Krook, (1947) Acta. Chir. Scand. Supp. 125, p. 13.
(P. E. Norstedt & Söner, Tryckerigatan 2, Stockholm.)

TABLE 2.

Frequency of intestinal obstruction and distress after different laparotomies.

Year	Author	Laparatomy for	No. of cases	In % of number of cases: Ob struc-tion	Of which late obstruction	Dis-tress	Of which op.	Comments
1914	Payr	Surg. dis.	3000	—	—	12—15	3,3	Not followed up
1929	Ranzi	„ „	2100	1.8	—	—	1.3	
1932	Peters	Peritonitis	—	5	—	13 consid. 12 slight	—	Followed up
1935	Kaufman	Surg. dis.	6500	0.5	0.4	—	0.4	
1944	Koch	Ulc. perf.	187	—	1.6	—	—	
„	„	Ventr. dis.	1259	—	0	—	—	Not followed up
„	„	Bile-tract dis.	1585	—	0.06	—	—	
„	„	Liver rupture	24	—	4	—	—	
„	„	Spleen rupture	13	—	8	—	—	
1906	Turner	Appendicitis	2500	1.9	0.8	—	—	Not followed up.
1911	Ruge	App. abscess	2385	1.2	0.9	—	—	Both op. and unop.
1918	Wolf	„ „	250	4.4	1.6	—	—	Some followed up
1926	Carlson + Marshall	Appendicitis	875	2.4	1.3	—	—	Not followed up
1932	Peters	Diff. app. perit	—	—	—	34	—	
„	„	Circumscr. app. perit.	—	—	—	15	—	Followed up
„	„	App. abscess	—	—	—	8	—	
1944	Koch	App. (no drain)	5966	—	0.2	—	—	Not followed up
„	„	App. (drain)	1388	—	2	—	—	
„	„	App. perit.	120	—	0.8	0	—	Followed up
„	„	App. abscess	100	—	3	6	0	
1922	Martins	Gyn. dis.	754	0.5	—	—	—	Some followed up
„	„	Adnex inf.	62	—	—	5	—	Followed up
1924	Heudorfer	Cyn. dis.	4559	0.3	0.1	—	—	Not followed up
1930	Holtz	Salpingitis	231	0	0	42 (15 of which salp. or loss of function)	—	Followed up
1932	Apojalahti	Tubal preg.	210	1.4	—	37 (26 of which prob. scalp.)	—	„ „
1933	Turunen	Gyn. dis.	1566	0.7	0.3	34	—	„ „ 1920–25
„	„	„ „	775	0	0	26	—	„ „ 1925–29
1944	Koch	„ „	3650	—	0.4	—	—	Not followed up

By kind permission of Dr. S. S. Krook, (1947) Acta. Chir. Scand. Supp. 125, p. 13.
(P. E. Norstedt & Söner, Tryckerigatan 2, Stockholm.)

TABLE 3.

Immediate results after treatment of intestinal obstruction.

Year	Author	All types of obstructions: No. of cases	Leth-ality %	Comments	Adhesions and bands: No. of cases	Leth-ality %	Comments
		Without use of intestinal intubation:					
1906	Wilms	1074	44	From 11 hosp.	104	55	From 6 hosp. Appr. fig.
1908	Scudder	121	60	No ca. & hernia	61	51	Only late obstruction.
1920	Richardson .	118	42	„ „ „ „	46	43	
1920	Flesch–Thebesius .	368	51	Lethality excl. ca. and perit. 42 %	137	35	Solitary cases colon & early obstruction incl.
1921	Flint	70	29	No hernia	39	26	
1925	Tuttle	128	41	Incl. ca. & hernia	33	39	
1925	Souttar	3064	26	From 7 hosp. Leth. excl. ca. & harnia 29 %	565	32	All internal strang. incl. Also colon obstruct.
1925	Perthes	203	36	Lethality excl. ca. 36 %	84	38	
1925	Braun	367	37	No ca. & hernia	154	34	All internal strang. incl.
1926	Holden	135	19	Lethality excl. ca. and hernia 15 %	46	20	Onle late obstruct.
1927	Braun	37	16	No ca. & hernia	14	7	All internal strang. incl.
1927	Moss et al .	171	71	Incl. ca. & hernia	46	65	
1929	Miller	343	61	„ „ „ „	98	58	Died, unop. incl.
1930	Holden	177	19	„ „ „ „	64	14	Only late obstruct.
1932	Vidgoff	266	46	„ „ „ „	170	38	
1932	Vick	6892	26	From 21 hosp. Incl. ca & hernia	1295	34	All internal strang. incl. Also colon obstruct.
1932	Cornell	235	52	Incl. ca., hernia & unop.	105	42	All op. on
1933	Mc Iver	156	44	No. ca. & hernia	68	32	Only late obstruct.
1934	Moss et al .	340	32	Incl. ca. & hernia	91	35	
1934	Christopher et al	2345	47	From 7 hosp. Incl. ca. & hernia	445	42	From 5 hosp.
1936	Röbbelen	103	49		79	41	
1938	Ivachnenko et al	608	39		—	28	
1938	Todyo	342	32		122	29	
1943	Korn	154	18		46	22	
1944	Koch	—	—		156	25	No TB cases. Only late obstruct. op. 1920—39
1947	Own material	—	—		426	20	Collected material Only late obstruction op. 1920—39
1947	Own material	—	—		43	5	Only late obstruction op. 1943—46. (In addition 1 pat. died. unop. a few hours after entry)
		Without use of intestinal intubation:					
1939	Kennedy et al	139	24		—	—	
1939	Wangensteen et al	156	18	Incl. ca. & hernia Corrected lethality	—	—	
1940	Whipple	76	13		43	7	
1940	Mc Kittrick et al	136	20	No. ca. or hernia	77	16	
1940	Johnston	63	19		—	—	
1941	Mc Kittrick .	22	9		—	—	
1943	Dennis et al.	110	16		—	—	

By kind permission of Dr. S. S. Krook, (1947) Acta. Chir. Scand. Supp. 125, p. 13.
(P. E. Norstedt & Söner, Tryckerigatan 2, Stockholm.)

TABLE 4.

Lethality in relation to duration of symptoms.

(Other types of obstruction than those due to adhesions and bands also included.)

Year	Author	No. of cases	Lethality percentage at time of anamnesis, hours			
			Under 24	24—48	Under 48	Over 48
1920	Richardson	100	—	—	33	48
1929	Brill	75	6	61	26	50
1932	Vidgoff	266	—	—	36	56
1933	Mc Iver	156	17	35	—	60
1943	Dennis et al	110	8	10	9	20
1944	Koch	156	10	29	15	50

TABLE 5.

Lethality in relation to mean age and mean duration of symptoms.

(Other types of obstruction than those due to adhesions and bands also included.)

Year	Author	Material from the period	No. of cases	Mean age	Mean duration of symtoms	Lethality %
1934	Moss et al	1923—27	171	—	1.8 d	71
1932	Cornell	1930—30	235	32 years	3.9 d	52
1939	Kennedy et al.	1924—31	86	43 years	2 d	35
1934	Moss et al	1930—32	340	—	1.5 d	32
1938	Rochkind	—37	108	44 years	—	32
1940	Mc Kittrick et al	—37	136	33 years	2.8 d	20
1939	Kennedy et al.	1932—38	105	40 years	2.5 d	25

TABLE 6.

Lethality in relation to the Age.

(Other types of obstruction than those due to adhesions and bands also included.)

Year	Author	No. of cases	Lethality percentage in the age-classes							
			Under 1	1-10	11-20	21-30	31-40	41-50	51-60	61-70	71-80
1920	Richardson	118	73	17	28	13	56	40	55	56	33
1933	Mc Iver	156	60	45	29	30	25	55	62	62	78

By kind permission of Dr. S. S. Krook, (1947) Acta. Chir. Scand. Supp. 125, p. 13. (P. E. Norstedt & Söner, Tryckerigatan 2, Stockholm.)

TABLE 7.

Lethality after different operative intervention against intestinal obstruction.

(Other types of obstruction than those due to adhesions and bands also included.)

Year	Author	Relief of obstruction	Relief obstr. + enterotomy	Relief of obstr. + enterostomy	Enterostomy	Anatomosis	Resection	Exteriorization
1931	Starlinger	37	—	—	—	46	58	63
1933	Boland	23	—	46	74	—	73	—
1933	Mc Iver	19	—	55	58	—	78	69
1935	Fey et al	21	—	—	—	—	55	85
1938	Scudder et al	24	57	48	30	44	38	83
1938	Rochkind	18	72	—	—	42	39	100
1938	Ivachnenko	25	—	—	93	—	67	95
1940	Henry	17	—	39	100	—	57	—

TABLE 8.

Late results after operation for obstruction due to adhesions and bands.

Author Operation	No. of survivors	No. followed up	Late results: Good	Satisfactory	Bad	Of which reop.	Of which died at reop.
Königsberg, 1938							
Strangulation	43	40	19	9	12	5	2
Division of bands		22	10	5	7	1	—
Division of bands + appendect		9	4	2	3	2	1
Resection		9	5	2	2	2	1
Adhesions	30	22	8	3	11	2	—
Reduction		18	5	3	10	1	—
Reduction + appendect		3	2	—	1	1	—
Resection		1	1	—	—	—	—
Total obstruction due to strangulations and adhesions	73	62	27	12	23	7	2
In % of the number followed up		100	44	19	37	11	
Clairmont and Meyer, 1929							
Adhesions and bands	31	19	(12 completely free from distress, 2 mild distress, 2 recurrences, and 3 deaths during period of observation)				

By kind permission of Dr. S. S. Krook, (1947) Acta. Chir. Scand. Supp. 125, p. 13. (P. E. Norstedt & Söner, Tryckerigatan 2, Stockholm.)

TABLE 10.

Appendicitis-peritonitis material: Early and late results.

	Total	Deaths connected with op.	Not followed up	Followed up (int. obstr. and distress)				O
				Int. obstr.	R.W.C.	C.D.	Inc. D.	
No. of cases	417	81*	20	13*	3	20	54	227
In % of total cases (417)	100	19	5	3	1	5	13	54
In % of cases followed up (317)	100	—	—	4	1	6	17	72
In % of cases followed up and found free of int. obstr. (304)	100	—	—	—	1	7	17	75

* One patient in common.
R. W. C. = Reduced working capacity.
C. D. = Considerable distress.
Inc. D. = Inconsiderable distress.

TABLE 20.

Original material of intestinal obstruction: Frequency of bands by sex and age.

	Sex	Total	Age, years 0—5	6—20	21—40	41—80
	M	234*	6	80*	64	84
No. of cases	F	173	5	24	59	85
	M + F	407	11	104	123	169
	M	177	5	66	46	60
No. of cases with bands ...	F	122	4	15	40	63
	M + F	299	9	81	86	123
	M	76	83	83	72	71
Cases with bands in % ...	F	71	80	63	68	74
	M + F	74	82	78	70	73

* One case with incomplete data omitted.

TABLE 21.

Original material of intestinal obstruction: Lethality, frequency of recurrence and distress in cases with and without bands.

	Cases with bands			Cases without bands		
	M	F	M + F	M	F	M + F
No. of cases	177*	122	299	57	51	108
Died in connection with op.	39	19	58	13	11	24
Followed up	135*	94	229	40	39	79
Recurrences	18	10	28	8	7	15
Distress (R. W. C., C. D., Inc. D.) ...	44	40	84	13	16	29
Deaths in % of No. of cases	22	16	19	23	22	22
Recurrence in % of No. followed up	13	11	12	20	18	19
Distress in % of No. followed up without recurrence	38	48	42	41	50	45

By kind permission of Dr. S. S. Krook, (1947) Acta. Chir. Scand. Supp. 125, p. 13. (P. E. Norstedt & Söner, Tryckerigatan 2. Stockholm.)

* One case with incomplete data omitted.
For R. W. C. etc. see under Table 10.

TABLE 24.

Original material of intestinal obstruction: Grouping by possible cause of obstruction.

	Total	Died in connection with op.	Not followed up	Followed up (Recurrence and distress)			
				Recurrence	R.W.C.C.D.	Inc. D.	O
Previously operated upon:							
Appendectomy	30	2	—	9	7	6	6
Appendicitis gangr. op.	29	5	—	1	4	4	15
Appendicitis-peritonitis op.	63	11	3	3	14	9	23
Appendicitis-abscess op.	26	5	1	3	4	3	10
Unspecified appendix op.	10	3	2	2	1	—	2
Gynecol. op. for T. B.	3	1	—	2	—	—	—
Gynecol. op. for other inf.	13	—	2	4	2	1	4
Gynecol. op. for not inf.	34	7	2	3	5	7	10
Hernia op.	30	8	2	4	1	2	13
Abdom. T. B. (op. for this or other disease)	19	1	—	7	4	1	6
Pulmon. T. B. (op. for other disease)	6	—	—	1	2	2	1
Meckel's diverticulum (op. for other disease)	4	1	—	3	—	—	—
Intussusception op.	5	1	—	3	—	—	1
Volvulus op.	4	2	—	—	1	—	1
Ulcus gastroduoden. op.	8	2	—	—	1	3	2
Bile-tract op.	5	2	—	—	—	1	2
Intestinal rupture op.	4	—	—	—	1	—	3
Spleen rupture op.	1	—	—	—	1	—	—
Mesenteritis op.	2	—	—	—	—	1	1
Obstr. adhes. colon op.	1	—	—	—	1	—	—
Obturation obstruction op.	1	—	—	1	—	—	—
Explorative laparotomy	3	—	—	1	1	—	1
Unspecified op.	1	1	—	—	—	—	—
Not previously operated upon:							
Abdom. T. B.	28	5	—	3	6	4	10
Pulmon. T. B.	2	—	—	1	—	—	1
Meckel's diverticulum	26	7	—	2	3	3	11
Appendicitis	8	2	—	1	—	2	3
Hernia	2	1	—	—	—	—	1
Salpingitis	5	—	1	—	—	1	3
Ovarian cystoma	1	1	—	—	—	—	—
Mesosigmoiditis	1	—	—	—	—	—	1
Lymphogranuloma inguinale	1	—	—	—	—	—	1

By kind permission of Dr. S. S. Krook, (1947) Acta. Chir. Scand. Supp. 125, p. 13. (P. E. Norstedt & Söner, Tryckerigatan 2, Stockholm.)

TABLE 25.

Original material of intestinal obstruction: Lethality, frequency of recurrence and distress within the different aetiological groups.

	No. of cases	Mean age, years	Mean duration of symp.	Lethality %	Recurrence in % of No. followed up	Distress in % of No. followed up without recurrence
Appendectomy	30	25	1.8	7	32	68
Appendicitis gangr. op.	29	32	1.4	17	4	35
Appendicitis-peritonitis op.	63	31	2.1	17	6	50
Appendicitis abscess op.	26	27	2.2	19	15	41
Gynecol. op. for inf. (not T. B.)	13	36*	2.9	0	36	43
Gynecol. op. but not for inf.	34	44**	3.6	20	12	55
Hernia op	30	55	2.3	27	20	19
Meckel's diverticulum (all)	30	25	2.5	27	23	35
Intussusception op.	5	8	1.4	20	75	0
Abdom. T. B. with previous op. (incl. gyn.)	22	31	1.6	9	45	45
Abdom. T. B. without previous op.	28	24	1.9	18	13	50
Pulmon. T. B. (all)	8	29	2.0	0	25	67
All previously op. on except appendix, gyn., hernia, Meckel's div. intussuscept., T. B.	30	43	1.7	23	9	52
All not previously op. on except Meckel's div., T. B.	97	46	2.0	27	5	35

TABLE 39.

Early and late results after resection, side-to-side and end-to-end anastomoses. [1]

	No. of cases	Deaths in connection with op.	Not followed up	Followed up (recurrence and distress) Recurrence	R.W.C.D.	Inc. D.	O
Resection, side-to-side anas. No.	38	13	—	3	9	5	8
Resection, end-to-end anas. No.	22	7	2	3	4	3	3
Resection, side-to-side anas. %		34a)		12b)	41c)	23c)	36c)
Resection, end-to-end anas. %		32a)		23b)	40c)	30c)	30c)

* Youngest patient 19 years, eldest 53.
** Youngest patient 21 years. Only two patients over 60 years.

a) of No. of cases. b) of No. followed up. c) of No. followed up without recurrence.

By kind permission of Dr. S. S. Krook, (1947) Acta. Chir. Scand. Supp. 125, p. 13. (P. E. Norstedt & Söner, Tryckerigatan 2, Stockholm.)

TABLE 40.

Original material of intestinal obstruction: Frequency of resection within the different aetiological groups.

	No. of cases	Resection	
		No.	%
Appendectomy	30	2	7
Appendicit. gangr. op.	29	3	10
Appendicit.-peritonit. op.	63	9	14
Appendicit.-abscess op.	26	2	8
Unspecified appendix op.	10	1	10
Gynecolog. op. for inf. (not T. B.)	13	1	8
Gynecolog. op. but not for inf.	34	3	9
Hernia op.	30	2	7
Meckel's diverticulum (all)	30	5	17
Intussusception	5	—	0
Abdom. T. B. with previous op. (incl. gyn.)	22	—	0
Abdom. T. B. without previous op.	28	2	7
Pulm. T. B. (all)	8	—	0
All previously op. upon except appendix, gyn., hernia, Meckel's div., intus., T. B.	30	1	3
All previously non-op. except Meckel's div., T. B.	97	9	9

One and the same case may occur in more than one row of the table, **viz.** if more than one operation or disease is mentioned in the case history.

By kind permission of Dr. S. S. Krook, (1947) Acta. Chir. Scand. Supp. 125, p. 13. (P. E. Norstedt & Söner, Tryckerigatan 2, Stockholm.)

CHAPTER VIII.

A. MODERN STUDIES AND VIEWS ON ADHESIONS.

Causation and prevention of Adhesions.

Much work has been done and many opinions expressed on ways and means of preventing adhesions. Some of the more recent work and the conclusions reached will now be described.

Green (1946) interested himself more in the cause than prevention of abdominal adhesions. In his experience he found it "not at all uncommon to see a patient who has had three or four abdominal operations, the first for appendicitis, salpingitis, fibroids et cetera, and the remainder for adhesions." In a recent series of fifty cases which were re-operated by him, there were only two in which some type of intra-abdominal adhesions were not present.

He thinks that our surgical procedures are at fault, as he does not believe that so many patients suffered from diffuse peritonitis. If massive pathology were present at the first operation we would expect subsequent difficulties, but we are mostly interested in the "clean case".

The history of the patient is usually that of a major operation. For weeks or months there was good health, but then increasing abdominal discomfort developed, bloating and crampy pains. Finally malnutrition enters the picture as the abdominal pain is increased by food intake.

Investigation shows dysfunction of the intestine due to a twisted or obstructed loop of gut, and surgery is advised for the relief of adhesions.

Green (1946) calls the initial trauma "viscero-peritoneal insult," and says that a serofibrinous exudate forms, followed by a "sticky peritonitis". The peritoneal insult should be critically investigated.

The most essential thing of good surgical technique is kindness to tissues. Violent handling especially during exploration of the

peritoneal cavity, is the most common error. The surgeon often uses a glove to which innumerable talc particles adhere. Talc is abrasive, and causes localized peritonitis and adhesions follow later. Washing the gloved hand before touching the peritoneum is essential.

Inserting a hot gauze pack is a serious mistake. This is done to improve exposure, but thermal injury is often the result.

Unfortunately solutions are but rarely checked for temperature and are usually too hot for safe application.

Green (1946) maintains that the steep Trendelenburg position, the increased expiratory excursion during anaesthesia and the abdomen full of gauze packs, will cause a rasping to-and-fro motion. This combination can be compared with the use of an emery cloth to the visceral peritoneum. An hour or more of the process serves as a peritoneal insult, and results in traumatic peritonitis.

He further warns us against the use of towels along the wound edges, peritoneal clamps, and self retaining retractors. These cause adhesions along the line of closure of the wound. Unnecessary large incisions should be avoided.

Invagination of the stump after removal of the appendix should be avoided as the purse-string causes a suture peritonitis. This tends to adhere this area to an adjacent peritoneal surface.

In anastomoses and Meckle's diverticulum excessive suture material should be avoided.

Green (1946) condemns the practice of inserting foreign materials into the abdominal cavity to prevent adhesions. He finds no sound physiological reason for the instillation of foreign materials.

Early, active motion, and early rising he considers important factors in the prevention of adhesions.

To summarize his advice one can say that the common surgical errors are:

1. The use of talc covered gloves.
2. The use of hot packs with steep Trendelenburg position.
3. The use of skin towels, peritoneal clamps and self retaining retractors.

4. Failure to recognise suture material as a cause of suture peritonitis.
5. Inserting foreign materials into the abdomen to prevent adhesions.
6. Keeping patients in bed too long after operations.

B. AMNIOTIC FLUID.

Amniotic fluid (the whole fluid) was at first introduced intraperitoneally as a treatment. Later a further improved product came into use, the alcoholic precipitate which contained the active principle of the whole fluid, and which permitted producers to discard the residual proteins. It was specially prepared to eliminate foreign protein, and to stabilize and sterilize the product.

Johnson (1928) was the pioneer in this field, and Warren (1928) wrote an account of the experimental work on animals.

Johnson's efforts were further spent on determining the following:

1. The mode of action of amniotic fluid on peritoneal surfaces.
2. Whether the fluid could be applied to cavities lined by serous membrane.
3. Its use in preventing adhesions.
4. To what type of case it could be applied with safety.
5. The immediate and remote effects that it had post-operatively in the peritoneal cavity.

Warren's work (1928) proved that amniotic fluid reduced coagulation time by fifty per cent, and that it served as a lubricant. He found no evidence of foreign body reaction when it was used and it was not absorbed quickly. Traces of the fluid were found in the peritoneal cavity up to the third day after application.

There was evidence that amniotic fluid contained an enzyme because boiled fluid failed to give the protection experienced when the unboiled fluid was used.

With the application of amniotic fluid a mild local leucocytosis is produced subperitoneally. This suggests that it somewhat

simulates the natural lytic action of proteases, and in this way facilitates the process of resolution.

Animal experiments proved that it could be applied with beneficial effects to all serous cavities.

The results of its use as a prophylactic were observed in animals. In the prevention of adhesions Johnson (1928) found that:

Thirty per cent of animals were completely protected against adhesions.

Another thirty per cent showed less than a hundred but more than fifty per cent protection.

Finally thirty per cent showed fifty per cent or less protection. He was encouraged sufficiently by the results to recommend the use of amniotic fluid in clean cases. He also reports excellent post operative recoveries where it was introduced into a small number of infected peritoneal cavities.

The amniotic fluid used by Johnson (1928) was prepared from certified cows three to five months pregnant and was processed by the Lilly Research Laboratories. No difference in action was found between human and cow amniotic fluid.

In Tables I and II he reports clinical cases treated with amniotic fluid.

Results of treatment can be obtained in three ways:

(a) Estimation from clinical observation.

(b) Inspection at subsequent operations such as repeated caesar sections.

(c) The occasional autopsy.

In his series postoperative observations recorded early return of peristalsis and hastened resolution. Return of peristalsis was evident from early expulsion of flatus, less distension than usual, and less post operative vomiting. On deep palpation on the fourth post operative day there was lack of pain or tenderness.

The amniotic fluid was introduced into the peritoneal cavity at body temperature. It caused no delay in healing of wounds. To substantiate this fact amniotic fluid was poured over abdominal wounds before closure.

Johnson (1928) summarizes his findings by saying that:

1. Its use has eliminated fear of reaction or infection.
2. Human and cow amniotic fluid have identical effects.
3. The mode of action is not completely understood, but it reduces coagulation time and acts as a lubricant.
4. Amniotic fluid can be applied with safety to all serous membranes.
5. His conservative estimate of its effectiveness is 70 %.
6. It should be reserved for clean cases.
7. It shortens post operative convalescence.
8. His series of clinical cases presented offers sufficient proof that the use of amniotic fluid is safe.

Although Johnson achieved good results with amniotic fluid, Lacey (1930) repeated the experiments and could not attain the same results.

Lacey thought that amniotic fluid could modify the density of the adhesions.

C. DIGESTIVE FERMENTS.

Pepsin and Trypsin.

There are certain agents which can help the surgeon to limit the formation of adhesions, but these do not solve the problem.

Jones & McClure (1929) state that the solution should be found if nature's method of prevention and ablation of adhesions is imitated.

With this principle in mind, Yardumian and Cooper (1934) studied the biochemical action in the development and retrogression of abdominal adhesions.

In spite of much controversy, they thought that the route of absorption did not matter much in this study. More important to them was that absorption takes place with great rapidity. This fact should be remembered when solutions are used to prevent the formation of adhesions.

Lacey (1930) found that in the early reaction to an inflam-

TABLE 1.

Analysis of series of 65 caesarean sections; abdomen filled with whole amniotic fluid or concentrate.

	Primary Indication for Caesarean Section	No. of Operations	Adhesions seen at Operation	Post Op. Cond.	Clinical Perit.	Deaths
Single laparotomy by Writer	Contracted Pelvis	26	None	Good	0	0
	Nephritic Toxemia	5 [3]	None	Good	0	0
	Previous Extensive Perineal Repair	3	None	Good	0	0
	Placenta Previa, Severe Hemorrhage	3	None	2 Fair 1 shock	0	0
	Previous Caesarean Section [1]	2	1 Moderate 1 Extensive	Good	0	0
	Disproportion	1	None	Good	0	0
	Ruptured Uterus	1	None	Fair	0	0
	Total	41	—	—	0	0
Reopenings	Contracted Pelvis	22	1 Ext. 1 Mod. 5 Slight, 15 None	Good	0	0
	Nephritic Toxemia	0	0	0	0	0
	Previous Extentive Perineal Repair	1	None	Good	0	0
	Placenta Previa, Severe Hemorrhage	0	0	0	0	0
	Previous Caesarean Section	0	0	0	0	0
	Disproportion	0	0	0	0	0
	Ruptured Uterus	1	None	Poor	0	0
	Total [2]	24	—	—	0	0
	Grand total	65			0	0

By kind permission of Dr. H. L. Johnson, (1928) New Eng. J. M. **119**, 661. (New Eng. J. Med. 8 Fenway, Boston 15. U. S. A.)

[1] One case showed extensive adhesions between scar and omentum. The other case showed extensive matted adhesions between parietal peritoneum about scar, omentum, and anterior surface of uterus.

[2] Two cases showed a delicate strand of adhesion between lower border of the omentum and the abdominal scar. On case showed additional small strand to uterine scar.

[3] One case had patient's fluid removed and 50cc "concentrate" substituted.

TABLE 2.

Clinical observations on 30 clean laparotomies treated with amniotic fluid concentrate.

Preoperative Diagnosis	No. of Cases	No. of Prev. Laps.	Condition of Peritoneum at Operation	Operations Performed	Kind & Quant. of Fluid	Immediate Post op. Condition	Early Convalescence			Clinical Peritonitis	Deaths
							Emesis	Flatus	Local Tenderness		
Appendicitis	22	3	3 with dense adhesions between omentum bowel and old scar	Append. 22 Oophor. 7 Enucleation of Fibroid 1	Whole 20 cc 4 Conc. 25 cc 18	Good	Severe 2 Mod. 4 Slight 16	Early expulsion 19 Late 3	Eearly Disappearance 22	0	*1
Cholecystitis	1	0	Good	Cholecystectomy Append.	Conc. 25 cc	Good	Slight	Early expulsion	Early Disappearance	0	0
Ovarian Cyst	2	1	2 with dense adhesions between omentum bowel and old scar	Oophor. 2 Append. 1 Salping octomy 1	Conc. 30 cc 1 50 cc 1	Good	Mod. 1 Slight 1	Early expulsion 2	Early Disappearance 2	0	0
Intestinal Obstruction	1	1	Dense adhesions between caecum and old scar	Lysis of Adhesions	Whole 20 cc	Good	Mod.	Early expulsion	Early Disappearance	0	0
Endocervicitis	1	0	Good	Hyster Append. Rt. Oophor. Rt. Salping	Conc. 50 cc	Fair	Slight	Early expulsion	Early Disappearance	0	0
Umbilical Hernia	1	0	Good	Herniorraphy Appendicectomy	Conc. 20 cc	Good	Slight	Early expulsion	Early Disappearance	0	0
Uterine Fibromata	1	1	Extensive dense adhesions between omentum bowel and old scar	Enucleation of Fibroid Lt. Oophor. D & C	Conc. 50 cc	Good	Slight	Early expulsion	Early Disappearance	0	0
Carcinoma of Cervix Uteri	1	0	Good	1 anhysterectomy	Conc. 50 cc	Fair	Slight	Early expulsion	Early Disappearance	0	0

By kind permission of Dr. H. L. Johnson, (1928) New Eng. J. M. 119, 661. (New Eng. J. Med. 8 Fenway, Boston 15. U. S. A.)

* Death due to Mesenteric thrombosis. Diagnosis confirmed by post mortem inspection through operative wound.

matory process there is found a local leucocytosis. Through the action of a proteolytic ferment derived from the leucocytosis the exudate of the inflammatory process is absorbed. Consequently there is dissolution of the material which could be the ground work for the formation of adhesions.

Experimental work: Yardumian & Cooper (1934) decided to use pepsin as a digestant, but decided to exclude pregl in the material used.

The Iodine contained in pregl had been shown to be a peritoneal irritant, and this might have counteracted all the beneficial effects of pepsin. (Payr (1922) was the first to use pepsin-pregl. Pepsin as a digestant and pregl, an iodine solution, was added to sterilize the ferment).

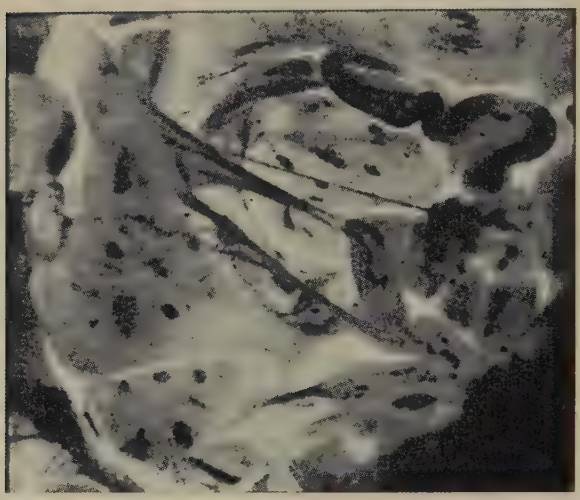
Having decided to use pepsin alone they used forty four animals on which one hundred and four laparotomies were performed. They found pepsin with glycerine and water extract more affective than pepsin with hydrochloric acid.

They performed five series of operations, and the following table shows their results.

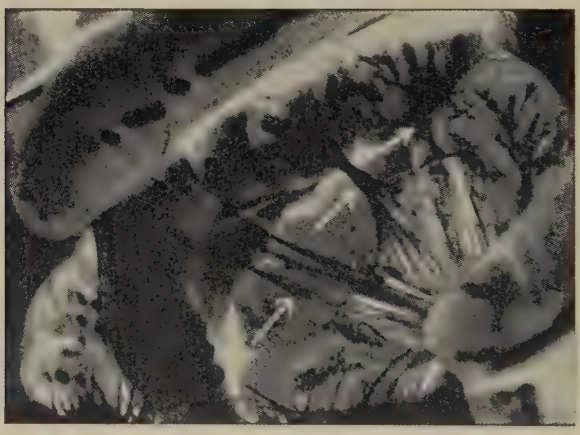
	No. of operations performed	Pepsin	% with no adhesions
Group 1	19	+ Hcl + Glycerine & water	25 %
Group 2	22	+ Glycerine & water	39.1 %
Group 3	22	+ Glycerine & water	86.4 %
Group 4	21	+ Glycerine & water	33 %
Group 5	20	+ Glycerine & water	25 %
Total, Groups 1—4.	85.		Average 45.8 %.

Yardumian and and Cooper (1934) comment that there is some hope in the solution of the problem of the formation of adhesions. Adhesions were considerably lessened, but they stress the necessary prophylactic measures in surgery in the prevention of adhesions.

Ochsner and Garside (1932) found that traumatized animals treated with trypsin showed adhesion formation in 9.09 % cases.

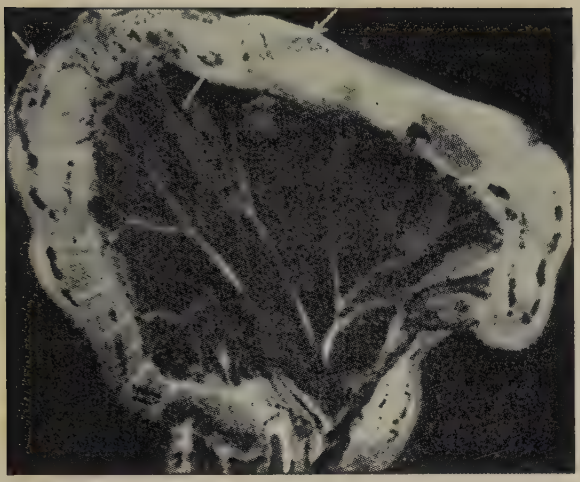


Twenty-two days after irritation and an injection of 50 cc. of 0.5 per cent of pepsin in a solution of glycerin and water. The one fine adhesion between the small bowel and the appendix can be seen.

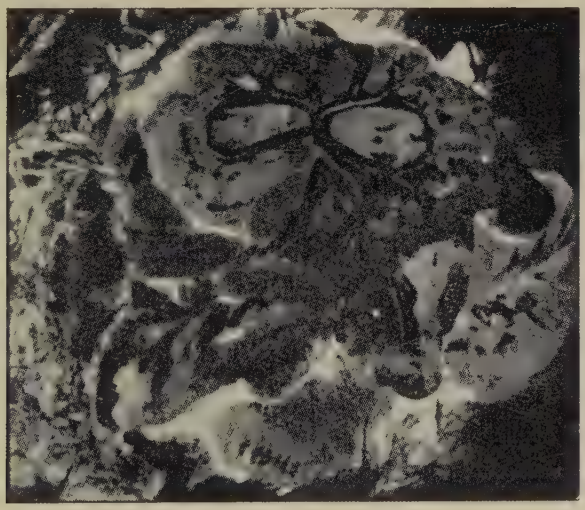


Operation thirteen days after a primary irritation (the small bowel was torn in the process and was repaired). Fifty cubic centimeters of pepsin in a solution of glycerin and water was injected. The repaired section of the bowel is adherent to the lower angle of the incision, and there are numerous cobweb adhesions.

By kind permission of Dr K. Yardumian (1934). Arch. Surg. **29**, p. 564. (The American Med. Ass. 535 N. Dearborn St., Chicago, 10.)



Operation twenty-four days after a primary operation, when the tissues were irritated. Fifty cubic centimeters of 0.5 per cent of pepsin in a solution of glycerin and water was injected. There are scars on the irritated section of the small bowel free from adhesions; edema of the mesentery is evident.



Operation thirty days after a primary irritation. Fifty cubic centimeters of 0.5 per cent of pepsin in a solution of glycerin and water was injected. The absence of adhesions is noticeable.

By kind permission of Dr K. Yardumian (1934). Arch. Surg. **29**, p. 564. (The American Med. Ass. 535 N. Dearborn St., Chicago, '10.)

Re-operated dogs treated with trypsin formed 57.63 % adhesions. Following the division of pre-existing adhesions, adhesions re-formed in 100 % of cases.

If these cases are treated with trypsin, few or no adhesions formed in 42.28 %.

They state in their conclusions that it is evident that digestive ferments are certainly of value in preventing the reformation of adhesions.

D. PAPAINE.

Papaine is a vegetable enzyme and it is obtained from the unripe fruit of a papaw tree. It acts in alkaline media but also in neutral media. When dried, the juice forms a powder which resembles gum arabic, and from this the enzyme is extracted. (Ochsner and Garside 1932.)

This enzyme was originally used by Kubota (1922). He believed that it caused chemotaxis when introduced into the peritoneum, and that an increase of leucocytes resulted in the peritoneal fluid. In principle increased leucocytes would have a beneficial effect, as the resultant leucoprotease or enzyme derived from leucocytes should protect the peritoneum.

Since Kubota (1922) recommended its use, much attention has been given to papaine. Walton (1930) investigated this enzyme and believed it to be effective in the treatment of adhesions. He attributed its value to its direct proteolyic activity, and not to its indirect action as was believed by Kubota.

Ochsner and Garside (1932) proved that 9.08 % adhesions still formed in dogs which were re-operated for adhesions and thereafter treated with papaine. In traumatized animals they found that 6.25 % still formed adhesions in spite of treatment with papaine.

From their experiments Ochsner & Garside state in their conclusions that;

(a) Following division of pre-existing adhesions, reformation of adhesions were found in 100 per cent if untreated.

(b) If saline solution was added to the peritoneal cavity few or no adhesions formed in 13.32 per cent.

If a solution of papaine was added, few or no adhesions formed in 90.89 per cent of the animals.

They stated justifiably that digestive ferments were of value in preventing the reformation of adhesions. Ochsner & Storck (1936) reported 231 clinical cases in which papain solution was used to prevent the formation or reformation of adhesions. He thought that many of these cases had an "adhesion diathesis" because 122 of this group had been previously operated, and in 46.9 % of cases where records were traced the operations had been for adhesions or obstruction.

The observation period after the use of papaine was 12 months or longer in 82.1 % of cases. Results were given from 224 patients and classified as excellent, good, fair and poor. Observations may be tabulated as follows:

Total	Excellent	Good	Fair	Poor
224	186	13	17	8

Further, thirty seven cases were reoperated following papaine treatment. There were no adhesions in 22 cases, although they had massive adhesions before division of the adhesions and papaine treatment.

In 13 cases few adhesions were present but much less than those before papaine was used. In 2 cases many adhesions reformed. There was a close correlation between clinical and experimental results.

Clinical use of papaine gave 94.5 % satisfactory results.

Experimental observation after the use of papaine: 90.9 % satisfactory results.

None of the four deaths that occurred could be attributed to the use of papaine.

(Ochsner & Storck 1936.)

Bogart (1937) performed an experimental study of peritoneal adhesions on 38 rabbits. He used a solution of 0.08 % sodium citratate in distilled water. He added to this solution 25 mg. of papaine, and found it satisfactory in preventing adhesions. Bogart relied on the response of the defence mechanism, and endeavoured to prove that the solution acts directly on fibrin and prevents the formation of the end-product. He thought that the solution

could divert the reaction of the peritoneum in such a way that it would digest the fibrin formed.

Of 30 clinical cases in which papaine was used Bogart (1937) had two deaths from other causes, two showed poor results and in 26 cases excellent results were observed.

Elliott and Meleney (1937) reported 72 cases in which they divided adhesions during a period of four years. They subjected 34 cases to papaine treatment and treatment was omitted in 38 cases. The cases were essentially similar and the operations were performed by the same team. Their observations did not show encouraging results with the use of papaine. In spite of this they realized that a very long observation period is necessary for definite conclusions. This was pointed out by Ochsner and Storck (1932).

Elliott and Meleney (1937) stated that for evaluation of the final results on clinical cases, a control series of cases should be included in the observations.

E. THE USE OF STREPTOKINASE AND STREPTODORNASE.

The factors affecting the development of adhesions were studied by a series of experiments by Thomas, Green and Rhoads in 1950.

They standardized the method for production of adhesions so that all animals should have the same amount of disturbance of the peritoneum.

Mechanical trauma was employed and efforts were then made to alter the incidence of adhesions. To do this they used penicillin streptomycin, streptokinase and streptodornase by injection.

Their standardized method for the production of adhesions was performed by crushing the caecum with a Kelly haemostat for one minute. The omentum was then wrapped around the injured caecum. Thirty six rats were traumatized in this way. (See table.)

The drugs used did not prevent adhesion formation in a single instance, but the extent of adhesions formed was decreased by penicillin and streptomicin. (Thomas, Green & Rhoads, 1950.)

Tillett et al. (1950) were specially interested in the action of two haemolytic streptococcal filtrates obtained from broth cultures. They found that these two filtrates had a clot-dissolving action or action of lysis, as well as a liquefying property. They

Number of rats used	No of days. intraperitoneal injections given	Type of injection used
7	5 (one daily)	100.000 units Penicillin
7	5 (one daily)	$^1/_{64}$ to $^1/_2$ gm. streptomycin
2	5 (one daily)	100.000 units Penicillin + $^1/_{64}$ gm. Streptomycin
2	5 (one daily)	2 daily doses of 250.000 units procaine Penicillin in sesame oil

Total number treated
18

Number of controls
18

(Thomas, Green & Rhoads, 1950)

called the first filtrate streptokinase and found that it activates the enzyme fibrolysin which in turn causes dissolution of human blood clots.

The second filtrate was called streptodornase which contains des-oxyribo-nuclease. This substance causes liquefaction of des-oxyribo-nucleo protein, which is present in 30 to 70 % of the solid portion found in purulent material.

They recognised the early adhesion as a bloody coagulum on the traumatized peritoneum. Streptokinase was thus used in an attempt to produce lysis of the coagulum. Penicillin was used additionally to counteract infection which might occur. Streptokinase was found to be quite effective in its action against human clot, but quite ineffective in rats.

In this study 88 rats were used. Of these 48 received 5000 to 100.000 units streptokinase and streptodornase. The injections were given in single and repeated doses, and at different time intervals. Some were given with penicillin.

The formation of adhesions occurred in treated animals to the same extent as in control cases. Forty control cases were used. Results may be tabulated as follows.

No of rats used		Incidence of adhesions
Total 88		
48	treated	87.5 %
40	controls	90 %

In another group of 18 rats adhesions were produced and surgical lysis (or division) performed at a second operation. Streptokinase and streptodornase were than inserted intraperitoneally.

In 9 of these, 40.000 units of streptokinase and 19.000 units of streptodornase were given at the time of lysis and also on the following day. The rats that received lysis and a single dose showed 67 % decrease after the first lysis, and 100 % decrease after the second lysis.

They found that the addition of the agents did sot make a great difference to the statistical results.

They found in the entire group that surgical lysis gave an average decrease of 67 % and 91 % in the entire group at the first and second operations respectively. They thought that surgical lysis alone gave better results than any other method tried in this group of experiments.

In their conclusion they stated that streptokinase and streptodornase did not decrease the incidence of adhesions, but they may have diminished the extensiveness of adhesions.

F. REPERITONEALIZATION.

A general belief has arisen that reperitonealization of denuded areas after surgery will minimize the formation of adhesions.

Singleton, Rowe and Moore (1952) tested this impression by performing a series of experiments in dogs.

Their series consisted of five groups.

In Group 1 ten animals were used. The operation consisted of stitching peritoneal patches removed from the abdominal wall to the denuded areas. The raw areas were 1 cm. by 1 cm. removed from the terminal ileum. Interrupted 0000 silk was used for stitching.

In Group 2 ten animals were used. In some the raw areas were closed by simple suture, using 0000 silk, 80 cotton, 34 wire or 0000 catgut.

In Group 3 five animals were used and the denuded areas on the ileum were closed by plication in some animals. Again a variety of stitch material was used: 0000 silk, 34 wire, 80 cotton or 000 catgut.

In Group 4 ten animals were used and no stitching was em-

ployed. Large areas of parietal peritoneum only, were removed, and the abdomens closed.

In Group 5, five animals were used, denuded areas were created, and sutures were passed through the peritoneum. Silk 0000 was used, and the sutures were not tied. The results may be summarized by the following table.

	Denuded areas	Stitched areas
Group 1	few adhesions	More adhesions
Group 2	few or no adhesions	More adhesions
Group 3	few adhesions	Greater no. of adhesions
Group 4	none except one animal - mild	Present where abdominal wound was closed
Group 5	few adhesions	More adhesions. Stitches act as foreign body

It was noted in all experiments that adhesions were frequent in areas which had not been traumatized. (Singleton, Rowe and Moore 1952.)

In 1949 Chester, Bell and MacCorkle covered intestinal anastomoses in the dog with peritoneal grafts in an attempt to obtain additional security at the suture line. The raw surface of the peritoneal graft was placed outward. Adhesions formed to the grafts in 90 % animals after 2 weeks and after 6 weeks in 40 % of animals examined. Adhesions were equally numerous when the smooth surface of the peritoneal graft was placed outward.

In 1949 also, Robbins, Brunschwig and Foote reported experiments in dogs in which areas of parietal peritoneum were removed with a minimum of adhesion formation resulting. They also reported a series of abdominal operations in the human being in which large areas were left without peritoneal covering; postoperative intestinal obstruction from adhesions did not result.

In discussing these experiments Rhodes (1949) reported experiments which he and his associates had conducted in rats. They concluded that parietal peritoneum would regenerate in the rat, as would also visceral peritoneum provided it was removed with great care to avoid injury to the underlying layers.

They also found that when fine silk sutures were placed under the peritoneum and left untied no adhesions resulted, whereas

oversewing denuded areas on the rat's caecum with the same suture material often resulted in formation of adhesions.

Denuded areas left untreated formed adhesions less frequently. Rhodes suggested that reperitonealization would occur spontaneously in man with less formation of adhesions than when raw areas were sutured.

Singleton, Rowe and Moore (1952) say that peritonealization of gastro-intestinal suture lines may be of value in preventing leakage, and plication of intestinal loops may be useful in preventing obstructing angulations.

They have been unable to find evidence in the dog, however, that any form of reperitonealization lessens the incidence of adhesion formation. On the contrary, the results in their study suggest that adhesions are less apt to form when denuded areas are left untreated.

Robbins, Brunschwig and Foote (1949) found that extensive removal of areas from the parietal peritoneum, did not cause marked development of adhesions in dogs and in the human being.

Thomas, Green & Rhoads (1950) made an experimental study of oversewing denuded peritoneal areas. They made abdominal windows of methacrylate (lucite) which allowed them direct vision of the processes of the formation of adhesions.

These abdominal windows allowed a wide range of studies, especially the processes of adhesion formation.

They studied the omentum and other viscera with respect to an injured area, and made the following observations:

After a viscus is damaged sufficiently, it undergoes distension, loss of mobility and vasodilation occurs. They saw the prompt outpouring of a serosanguinous exudate which undergoes coagulation within a short period.

In the meantime the omentum and other viscera maintain their mobility. The omentum in particular seems to be either pushed or attracted to the sticky coagulum and then adheres to it.

They were able to bring under observation the process of adhesion formation very clearly, as they found that the viscera remained clearly visible beneath the abdominal windows for a period of one to three weeks.

Thomas, Green & Rhoads (1950) performed further experiments to determine the effectiveness of surgical lysis in preventing the

reformation of adhesions. In these experiments 150 rats were used in groups.

In Group I, they used 70 rats and adhesions were established in two ways.

In 31 they crushed the caecum and returned it into the abdomen.

In 39 they crushed the caecum and then wrapped the omentum around it before returning it into the abdomen. The latter resulted in denser adhesion formation.

In Group II, they used 27 animals and crushed the caecum in four different places to produce adhesions.

In 13 of these cases the caecum was wrapped in the omentum before replacing.

In the other 14 the caecum was replaced without wrapping round the omentum. The animals showed an average of 2.5 adhesions in each one, but the first method resulted in denser adhesions.

Results were the same in Group I and Group II and the method of adhesion production was found to be effective.

In those rats with single adhesions they found a 66 % decrease after the first lysis and a 90 % decrease after the second lysis.

In rats with multiple adhesions there was a 71 % decrease after the first lysis and a 93 % decrease after the second lysis.

Their conclusion was that simple division of adhesions proved to be the most effective means in their tests of lowering the incidence of mechanical produced adhesions in the rat. (Thomas, Green and Rhoads-1950.)

Removal of Serosa.

Thomas and Rhoads (1950) experimented on rats and guinea-pigs and found that oversewing bowel which is denuded of serosa, more than doubled the production of adhesions.

Reperitonealization or oversewing denuded areas in the peritoneal cavity has been a practice for many years. This impression was also tested by Singleton, Rowe and Moore (1952) and the results of their work are tabulated earlier in this chapter.

Thomas and Rhoads (1950) state that the usual practice is to approximate serosal edges with fine gut or silk using a round bodied needle and taking delicate bites. Often interrupted sutures are used.

Chandy (1950) proved that omentum commonly encapsulates silk. In his experiments he showed that silk in itself produced adhesions in rats.

Thomas and Roads (1950) used 55 male albino rats and 40 male guinea-pigs for experimental purposes. They used two groups.

Group A. These served as controls and were not oversewn. In the rats the caecum was the site selected, and in the guinea-pigs the terminal ileum was used for denudation. Denuded areas measuring 0.5 by 2 cm. were produced by means of a fine toothless forceps, and care taken to leave underlying tissues intact. After replacing the viscera they closed the abdomen with an everting black silk suture, and by the continuous method.

Group B. In this group the peritoneum was denuded in an identical manner, but 0000 black silk on a small atraumatic needle was used, and the denuded area was oversewn. The abdomen was closed in the same way. The animals were sacrificed on the sixth day and obduction performed. Adhesion formation is usually completed within 3 to 6 days after injury. (Richardson, 1911.)

The results of their work are best seen from their tabulated figures.

		No that formed Adhesions	No with no Adhesions	Percentage with Adhesions
Group A	Not oversewn			
	Rats	8	20	28.5
	Guinea-pigs	7	12	36.8
Total for Rats & Guinea-pigs:		15	32	31.9
Group B	Oversewn			
	Rats	20	7	74.0
	Guinea-pigs	18	3	85.7
Total for Rats & Guinea-pigs:		38	10	79.0

Figures from Thomas & Rhoads (1950) Arch Surg. 61 : 565.

Although Robbins, Brunschwig and Foote (1949) found that denuded areas in dog and man do not cause marked development of adhesions, Thomas & Rhoads' experiments prove entirely different results, as seen in their table. They show that 31.9 % of denuded areas form adhesions, and if oversewn 79 % form adhesions.

G. THE EFFECT OF SULPHANILAMIDES ON THE PERITONEUM.

Sulphanilamide has been a populair powder, and its intraperitoneal use is said not to produce adhesions. This view has been supported by considerable evidence from Ravdin et al. (1940), and Thompson et al. (1941).

Throckmorton (1941) and (1942) reported on studies of the response of the peritoneum to treatment with these powdered drugs. The smears from the fluid and exudate obtained by aspiration showed no specific reaction of the peritoneum. From experiments in rats he found that Sulphanilamide and Sulphathiazole did not create adhesions.

Jackson & Coller (1942) presented a series of experiments carried out on dogs. Sulphanilamide was implanted into the peritoneal cavity and the peritoneal fluid was later examined for cellular response. The peritoneal cavities were freuently examined; from four hours to one month later. They found no evidence of any specific reaction to the drug. In peritonitis, the improved clinical results were illustrated by Jackson & Coller (1942).

Eleven experiments were performed on 7 dogs by Laird & Stavern (1942) using Sulphathiazole and Sulphanilamide. They found that inflammation occurred with the use of Sulphathiazole but not with Sulphanilamide.

Harbison & Key (1942) discovered dense abdominal adhesions during the second operation of a two-stage procedure for resection of the caecum.

They were faced with the question whether sulphanilamide and its derivatives cause adhesions when introduced into the peritoneal cavity. The second question that arose was whether the adhesions were due to infection or to the presence of the powdered sulphanilamide.

Harbison and Key (1942) thus decided to carry out investigating experiments on a group of rats. Having given the rat a general anaesthetic, the abdomen was opened and 500 mg. of sterile sulphanilamide, powdered or crystalline, or one of its derivatives was introduced into the abdominal cavity.

The sulphanilamide was spread throughout the peritoneal cavity as well as possible by a blunt curette. The curette was also used

to cause a moderate amount of trauma to the visceral and parietal peritoneum.

The drugs employed were sulphanilamide, sulphathiazole, sulphadiazine and a mixture of two parts of sulphanilamide and one part of sulphathiazole.

Ten animals were used in the study of each drug and the mixture. Ten were used as controls. In controls the same curetting trauma was performed, but no drug was inserted into the abdomen.

The wounds of all animals healed by first intention. One animal died on the 22nd day from unknown causes. No adhesions were found at autopsy.

The other animals were killed after 28 days. Examination of the peritoneal cavities showed no adhesions in any of the animals in which the drug had been introduced. Occasional thin adhesions were seen from the omentum to the abdominal wound.

In the controls no adhesions were found except in two instances where omentum was again adherent to the abdominal wound.

Microscopic sections of the peritoneum of some animals were made. Examination of the sections showed no difference between treated and control cases. In all the sections the peritoneum appeared to be normal.

In 1943 Crutcher et al. performed experiments using fifty five dogs. Again the effect of Sulphanilamide, Sulphathiazole and Sulphadiazine was determined when placed into the peritoneal cavity. Prior to the operations it was noted that when finely powdered Sulphathiazole crystals were poured into the peritoneal cavities of dogs, part of the drug tended to become walled-off by the omentum.

It became a mass or lump which was quite hard when removed, and it was noted that this lump could persist for as long as four days. When the finely powdered drug was applied the incidence of hard lump formation was more frequent than when coarse crystals were used. Adhesions between intestinal loops were more frequently found when lumps occured. In 1942 Throckmorton stressed this fact in his study of the cellular response of various drugs in the peritoneal cavities of albino rats.

Crutcher et al. (1943) conducted more groups of experiments.

In Group 1 the fine powder of the drug was scattered over intestinal loops.

In Group 2 a suspension of the drug in 50 cc. sterile water was poured into the wound.

In Group 3 a weighed amount of drug was moistened with distilled water and then allowed to dry. A hard lump was formed which was broken into peices and placed between loops of intestine.

In all treatments 0.3 gm. per Kilogram of body weight was used, and was introduced by laparotomy under general anaesthesia. Sterile technique was used; the omentum was pushed upwards and the small bowel carefully examined for adhesions before starting treatment.

The abdomen was closed in layers with fine interrupted silk sutures.

Laparotomies were performed at varying intervals after introduction of the drugs. In some instances animals were sacrificed to perform examination, and in others laparotomy under anaesthetic was performed to examine for adhesions and the incision closed. There were no instances of wound infection.

The concentrations of the drug in the blood stream were determined at intervals by the method of Bratton & Marshall (1939).

The Results of their experiments:

Four animals served as controls and were subjected to operation, but no drug was inserted. Examinations after 5 to 15 days showed no adhesions. Their results and blood concentrations are tabulated below.

Crutcher et al. (1943) came to the following conclusions:

(a) Adhesions may be produced in the peritoneal cavity of the dog by the introduction of Sulphanilamide, Sulphathiazole and Sulphadiazine

(b) The drug may be responded to as a foreign body. It may be walled-off and then be absorbed very slowly.

(c) Even distribution of the fine powder should be practised to avoid lump-formation. To ensure this, suspension in sterile water or saline is preferable.

(d) Sulphadiazine produces greater local peritoneal reaction than sulphanilamide or sulphathiazole.

(e) Sulphadiazine is absorbed more slowly from the peritoneal cavity than the other drugs.

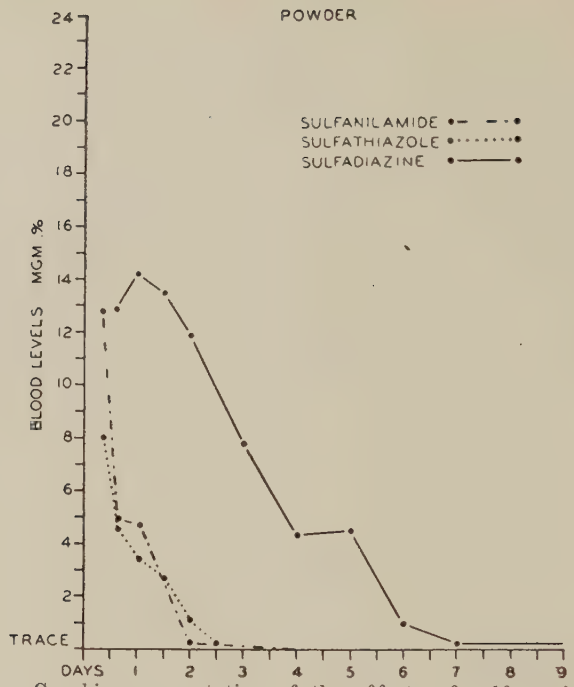


Chart 1. — Graphic representation of the effects of sulfonamide therapy on the blood concentration when applied as a powder.

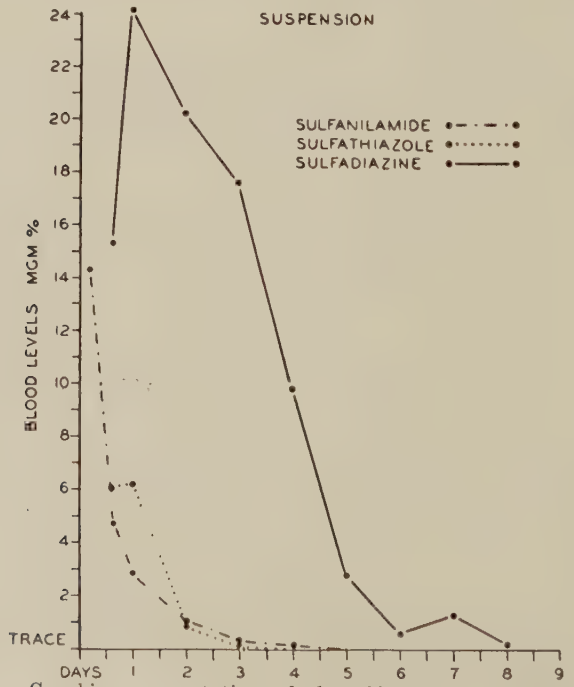


Chart 2. — Graphic representation of the effects of sulfonamide therapy on the blood concentration when applied in suspension.

By kind permission of Dr Richard R. Crutcher (1943). Ann. Surg. 117, p. 677. (J. B. Lippencott Co., Philad. 5, U.S.A.)

Sutton (1942) reported a case of acute gangrenous appendicitis in which sulphathiazole caused multiple adhesions when it was introduced into the peritoneum. Adhesions, intestinal obstruction and secondary operation followed. Sulphanilamide was also implanted into the abdominal wound, and resulted in delayed healing of the wound and a keloid scar.

Case History September 1941. A boy of ten, complaining of nausea and vomiting, pain in the Right Iliac Fossa. Temperature 101.2 F. Blood: leucocytosis 20.600 with 90 % polymorphs.

At Operation a thin purulent exudate was found in considerable amount, and gangrenous appendix with a small perforation. The peritoneum was injected but no adhesions could be found. The stump of the appendix was buried after appendicectomy. Three gm. of sulphathiazole crystals were sprinkled in the Iliac Fossa and on the peritoneum where abundant exudate was seen. A penrose drain was inserted. To the abdominal wound two gm. sulphathiazole was applied before closure.

After he had recovered from the anaesthetic, 0.5 gm. sulphathiazole was given by mouth 4 hourly. The drain was removed on the 5th day. For the first 72 hours sero-sanguinous fluid was discharged. Troublesome bladder irritation also occurred for several days due to sulphathiazole. Wound healing was retarded until the 28th day, and by that time the scar was thick and elevated.

He was discharged on October 14, but one month later attacks of abdominal cramps began. Progressively they became worse and more frequent. Definite symptoms of obstruction with nausea and vomiting occurred on Dec. 14, and he was admitted to hospital. Operation revealed a loop of ileum adherent to the parietal peritoneum posterior to the caecum. This produced kinking and obstruction. The omentum was adherent to the parietal peritoneum at several places. It was also adherent to the ileum and caecum.

No other adhesions were present excepting in the area described below:

The peritoneum, over an area corresponding exactly to the area of application of the sulphathiazole, was covered with a granular, reddish tissue. In parts of the area this tissue was as thick as 2 to 5 mm. The surface appearance was that of pale granulation

EFFECTS OF SULFONAMIDE THERAPY

TABLE 1.

Finely powdered crystals.

	Exper. No.	Time of Examination after Drug Implantation	Number and Character of Adhesions	Visible Drug Remaining
Sulfanilamide	1	5 days	None	None
	2	5 days & 36 days	Slight 5 days; none 36 days	None
	3	5 days & 66 days	None	None
	4	11 days	None	None
	5	98 days	None	None
Sulfathiazole	18	4 days	None	None
	19	5 days & 6 months	None	None
	20	6 days	None	None
	21	9 days & 31 days	Marked 9 days; slight 31 days	None
	22	11 days	None	None
	23	22 days	None	None
	24	13 days & 91 days	None	None
	25	13 days	Slight 13 days; none 91 days	None
	26	13 days	None	None
	27	9 days	Slight	None
	28	13 days	None	None
Sulfadiazine	39	10 days	None	None
	40	8 & 45 days	Marked: 8 & 45 days	Several small lumps, 8 days
	41	10 & 45 days	Marked: 10 & 45 days	None
	42	8 & 45 days	Marked: 8 & 45 days	1 small lump, 8 days

TABLE 2.

Finely powdered crystals suspended in sterile distilled water (about 50 cc.).

	Exper No.	Time of Examination after Drug Implantation	Number and Character of Adhesions	Drug Remaining
Sulfanilamide	6	4 days	None	None
	7	4 days	2 small (omentum-bowel)	None
	8	7 days	None	None
	9	7 days	None	None
	10	7 days	None	None
	11	11 days	None	None
Sulfathiazole	29	9 & 31 days	Slight 9 days; none 31 days	None
	30	9 & 31 days	None	None
	31	9 & 31 days	None	None
	32	9 & 31 days	Slight: 9 & 31 days	None
	33	9 & 31 days	Slight: 9 & 31 days	None
Sulfadiazine	43	6 & 36 days	Marked: 6 & 36 days	None
	44	6 & 36 days	Moderate: 6 & 36 days	None
	45	12 days	Moderate	None
	46	12 days	None	None
	47	20 days	None	None
	48	28 days	None	None
	49	28 days	None	None

By kind permission of Dr. Richard R. Crutcher (1943). Ann. Surg. 117, p. 677. (J. B. Lippincott Co., Philad. 5, U. S. A.)

TABLE 3.

Lumps

	Exper. No.	Time of Examination after Implantation	Number and Character of Adhesions	Drug Remaining
Sulfanilamide	12	9 days	Moderate	None
	13	9 days & 34 days	Moderate	None
	14	9 days & 34 days	Moderate	None
	15	9 days & 34 days	Moderate	Small lump at 9 days
	16	8 days	None	None
	17	28 days	None	None
Sulfathiazole	34	5, 62 & 91 days	Marked: 5, 62 & 91 days Moderate 3 days;	1 large lump at 5 days
	35	3 & 37 days	none 37 days	4 small at 3 days
	36	12 days	Moderate	None
	37	20 days	Moderate	None
	38	37 days	Moderate	2 small lumps
Sulfadiazine	50	20 days	Marked	1 large lump
	51	20 days	Marked	None

By kind permission of Dr. Richard R. Crutcher (1943). Ann. Surg. 117, p. 677. (J. B. Lippincott Co., Philad. 5, U. S. A.)

tissue and was attached to the surface of the peritoneum. The serosal tissue was not invaded.

Omental adhesions and that of the ileum were freed and abnormal tussue excised for study. The wound was closed without drainage.

Microscopically the abnormal tissue showed dense connective tissue and small blood vessels. Sulphathiazole crystals were absent. The tissue was microscopically diagnosed as collagenous connective tissue. The abdominal scar showed the same type of tissue microscopically throughout all layers of the abdominal wall. This scar was excised at the operation for the obstruction. The area of abnormal tissue here again corresponded with the distribution of the sulphathiazole.

After the second operation (for obstruction) convalescence was uneventful, and the wound healed by first intention with a hair line scar. The patient was discharged on the 9th day, and two months later was still in good health.

Sutton (1942) comments that it seems reasonable to accept that this was an unusual tissue response to sulphathiazole. The patient had several other scars which showed no tendency to keloid thickening. Sutton did not think that the penrose drain could have caused the adhesions, as the adhesions occurred at divergent points only where the sulphathiazole had been placed.

Further Studies of Sulphanilamides in relation to peritoneal adhesions, and its combination with Heparin.

When applied locally, different effects on tissue were recognosed by Lyons (1942). He found that the reaction on tissue depended on the solubility of the drug used.

Boys and Lehman (1943) studied:

(a) The effects of Sulphanilamide and Sulphathiazole on the intact peritoneum of the dog.

(b) The rate at which adhesions reformed when Sulphanilamide was combined with Heparin.

Methods: Mature dogs were used, and aseptic technique was practised. Adhesions were created by scarification and were divided by sharp dissection six weeks later. Intraperitoneal haemostasis was effected by silk or cautery.

There were three groups of experiments.

1. *The effects of Sulphanilamide on the normal abdomen.*

   A. Control. The bowel and omentum were placed into a warm solution and replaced.

   B. Scarification was used in an attempt to create adhesions.

   C. Dry Sulphathiazole was introduced 0.5 grm. per kilogram of body weight.

   D. Dry Sulphanilamide was used.

2. *After Division of Adhesions:*

   A. Dry Sulphathiazole or Sulphanilamide were sprinkled over the involved portions.

   B. Concentrated sulphanilamide solution, saturated in saline was injected into the peritoneum for the three postoperative days. 150 cc were given daily in single and divided doses.

3. *Division of adhesions — Heparin and sulphanilamide.*

   A solution of heparin and sulphanilamide was injected into the peritoneum after the division of adhesions, on the three postoperative days. The total daily dose was a 150 cc solution which contained 1.2 gm. of sulphanilamide, and 30 mg. of

heparin. In some animals the amount was given once daily, and in others it was divided into two 12-hour doses.

Results.

1. With the use of dry Sulphanilamide the average number of adhesions formed was 1.6, which compared with an average of 1.1 in controls. In the Sulphathiazole experiments every animal presented at least one adhesion, but in Sulphanilamide eight out of fifteen animals presented no adhesions. Fifty one dogs were used in these experiments.

2. *Division of Adhesions — Sulphathiazole and Sulphanilamide.*
   In both experiments the use of a dry preparation resulted in more adhesions than were divided.
   With Sulphathiazole reformation was more than 225 %, with Sulphanilamide greater than 175 % and with Sulphanilamide solution the reformation rate was only 100 %.

3. *Division of adhesions — Heparin and sulphanilamide.*
   With the combination better results were seen. Results were also much improved in animals that received two injections daily. When given once daily, the rate of reformation was 73 % and when given twice daily it was 23 %.
   They came to the following conclusions:
   (i) That dry powder should not be inserted intraperitoneally into the human peritoneum.
   (ii) In solution Sulphanilamide offers less danger of peritoneal adhesions than the commonly used dry product.
   (iii) The experiments showed that the combination of sulphanilamide and heparin proved more effective as treatment in divided adhesions than sulphanilamides alone.

H. TALC AFFECTS ON THE PERITONEUM.

An interesting report from Glascow was given by MacKey and Gibson in 1948. They stressed the fact that talc powder is a cause of adhesions. In their experience soft and avascular adhesions were often seen after resolution of a bacterial inflammation. These adhesions were seen in an unopened abdomen. In reopened abdomens, after aseptic laparotomies had previously

been performed, vascular, dense and widespread adhesions were found in some cases. This fact suggested to them that laparotomy may occasionally introduce a substance more irritating than bacteria.

Their observations over fifteen years showed that talc was one of these irritants. Talc is a Magnesium trisilicate compound.

They mention two other authors who noted this fact and wrote about the harmful effects of Talc.

Eiseman, Seelig & Womack (1947) from America and Roberts (1947) in Britain.

MacKey and Gibson (1948) state that the action of talc results in a proliferative response which is comparable to that found in traumatic siliceous granuloma, or pseudo-tuberculoma silicotium. (Stattock (1916); Faulds (1935).)

The irritating results of talc implantation are not only found in the peritoneum but also in wounds. Granulomatous formation may be seen in scars; sinuses may form, faecal fistual, and stenoses of entero-anastomotic stomata.

Roberts (1947) wrote that talc could cause chronic fibrosis of the Fallopain tube with consequent sterility. He wrote that a case history, and the density of peritoneal adhesions seen at operation may suggest a different diagnosis. Siliceous granuloma may be suspected, but microscopic sections would show collagenous tissue, doubly refractile material with the appearance of talc closely related to foreign body giant cells.

He states that "polaroid" screens on an ordinary microscope are simple to use, and will leave no doubt as to the diagnosis. If sections are not examined for anisotropic material the condition may be mistaken for tuberculosis, regional enteritis, sarcoid disease, keloid scar, or non specific foreign body reaction; but the situation of the granuloma would be difficult to explain.

Foreign material such as sutures are often surrounded by giant cells, and may to some extent show the property of rotating the plane of polarized light, but they are unlikely to be spread diffusely over the peritoneum. The structure of talc as seen by polarized light is fairly characteristic. Many years after the implantation of talc into the tissues, it has still been seen in sections prepared by routine histological methods. (Roberts, 1947.)

Case History from MacKey and Gibson (1948).

Miss B., aged 74. Admitted to medical wards of the Western Infirmary, Oct. 3, 1937, for investigation of severe anaemia.

The Anaema developed over a period of 4 years. She was passing considerable quantities of altered blood in the stools.

Investigations, clinical, haematological and radiological could find no source.

Transfusion of 9 pints (5.1) litres of blood over a period of a month scarcely replaced the loss. Her condition remained serious.

It was decided to perform a laparotomy in the hope of finding the bleeding-point. She had undergone no previous operation.

First Operation Nov. 26. A right paramedian incision was made in the upper abdomen. Wide exploration was made. A Meckel's diverticulum attached to the umbilicus, was found. As it was not the source of bleeding it was not removed but freed from the abdominal wall. The spleen was enlarged to twice its normal size. The spleen was removed, and the arteries at the ends of both curvatures of the stomach were divided in the hope that the undisclosed lesion might be in the upper division of the portal system. The patient had an uneventful recovery from the operation, but bleeding into the alimentary canal continued. On several occasions aspiration of the stomach was carried out over long periods, but no blood was discovered. By December 9, the haemoglobin level had fallen to 38 % and it was decided to open the abdomen once more. In the absence of the Prof. the responsibility fell on one of the authors. The patient was prepared by transfusion of 4 pints (2.27 Litres) of blood.

Second Operation. This was performed on December 9th, thirteen days after the first operation. Dense adhesions of recent origin were present. They involved the stomach, omentum, the Meckel's Diverticulum and the anterior abdominal wall.

After removal of the diverticulum, inspection showed no ulceration which could cause bleeding. The small intestine contained altered blood in its entire extent. No ulcer or polyp could be palpated, but examination of the stomach was difficult due to adhesions. The abdomen was closed, the patient recovered and the haemoglobin was 82 % four days later. The bleeding continued and to date was unexplained.

Pathological Report on the Meckel's Diverticulum.

"The Peritoneum is dull, and the wall thick and dense. The mucosa has a normal velvity appearance. Histological sections show zones of thickly woven collagenous connective tissue external to the muscularis and extending into it here and there for a short distance. This tissue replaces most of the subserous fat, is responsible for the increased thickness of the wall, and forms the outer surface of the diverticulum at several places. Imbedded in it lie many foci of macrophages and foreign body giant cells, arranged in some instances in the form of poorly defined follicles. These cells surround brownish crystalline doubly refractile particles of an average length of 15 μ and of a shape identical with surgical talc. Similar material is seen underneath the serosa in varying concentrations in all parts of the diverticulum. The mucosa is of the normal small intestine type and no areas of gastric heterotopia are present."

In their comment MacKey and Gibson (1948) state that there is no doubt that these lesions orginated from the first operation thirteen days before the specimen was removed. Opportunity seldom occurs to remove a specimen so soon after an aseptic laparotomy, and they publish this report to show how quickly such dense fibrous adhesions may form in response to a small quantity of talc.

In a series of cases described by Eiseman, Seelig and Womack (1947) they show that several patients complained only a few days after operation of symptoms which were later ascribed to talc granuloma, but histological sections could not be taken in any of these cases until at least two months after the primary operation.

In the case of MacKey & Gibson (1948) there were no symptoms despite the extent and intensity of the reaction produced.

They were convinced that the use of talc at operation is a practice which subjects the patient to potentially grave consequences. The authors of the two reviews quoted above very emphatically recommend that the use of talc should be completely amandoned. They suggest two other materials: Pot. Bitartrate and Formolised starch which are free from irritant effect, but unfortunately they have disadvantages. A search for a completely satisfactory powder for gloves up to 1948 was not found. MacKey

and Gibson recommended that talc should be reduced to a minimum in its use, and that one should prevent its deposition into the peritoneal cavity.

It will be seen later in this study that there is a suitable substitute and that this should be used instead of talc.

Previous Studies on Talc.

Shattock (1916) described the first case of talc granuloma. The patient's lip was injured, and he subsequently developed a tumour in the scar. Microscopic examination proved that it was caused by Silica.

Antopol (1933) described 6 cases of foreign body granulomata in the peritoneal cavity. The granulomata were situated in the subserosa, and they contained refractile particles identified as talc.

Faulds (1935) described two cases of talc granuloma in scars in which the lesions were removed 10 and 23 years after injury. They proved that the lesions were due to the same slate (silica) present on the ground where the original accidents occurred.

Feinberg (1937) described several foreign body granulomata in scars from previous operations due to talc.

Seelig (1943) et al. investigated talc powder and stressed the fact that it caused adhesions. They suggested that potassium bitartrate should replace the use of talc.

Roberts (1947) reported 7 cases which had undergone previous operations and during which irritant material must have been introduced. In five cases the granulomata due to talc involved the fallopian tubes, and in two others the abdominal scars. Microscopic examinations varified that talc was the cause, and the giant cells and refractile particles were clearly demonstrated.

Weed & Groves (1942) found that perforations occurred in 22.5 % of 35,763 gloves which were used in 4,549 operations. He thought that these perforations occurred through a tear or puncture of a glove and that talc powder lying in the nail fold was then liberated onto the peritoneum.

Lee & Lehman (1947) stressed the irritant nature of talc powder. Experimentally they showed the uncountable, massive adhesion

formation when talc was dusted over the serosal surfaces. From sections of the regional lymph nodes they showed that talc was not absorbed via the lymphatics. They investigated several starch powders and their lubricating properties when sterilized. They demonstrated that powder 108 (Johnson & Johnson) was suitable to autoclave and retained its qualities of flow on surgical gloves. It absorbed completely from the peritoneum without forming adhesions.

Postlethwaite et al. (1949) did extensive work on the comparison of tissue reaction to talc and starch glove powders. They warned surgeons against talc, and the subsequent major operations which may follow its use. They described five sources of talc which may result in implantation:

(1) A tear or perforation in a glove.

(2) Unwashed gloves.

(3) Spilling powder onto instruments and sponges; e. g. from shakers or gloves.

(4) Airborn transmission when applying glove lubricant.

(5) From rising powder if swabs are thrown into a bucket containing the excess powder.

They studied the reactions of starch and talc on the peritoneum, pericardium and pleura and demonstrated their extensive reactions to talc and the negligible reaction caused by starch.

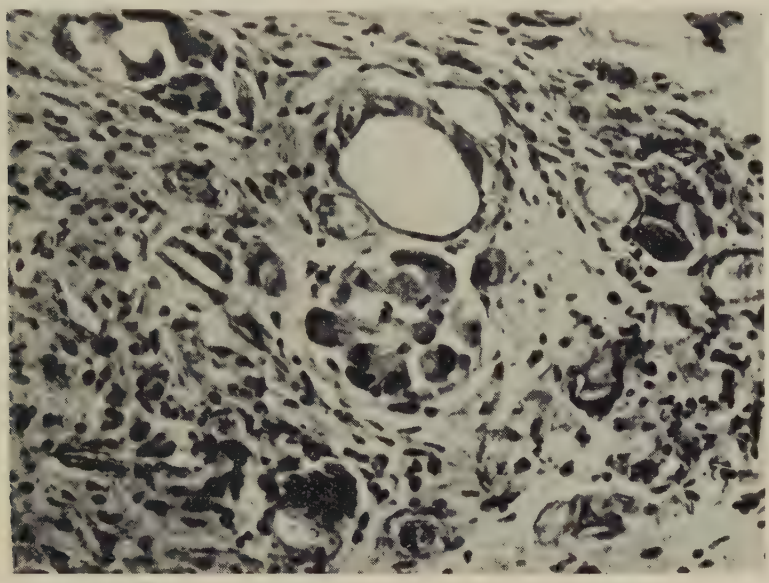
Both these lubricants were also implanted into tendon, joint, muscle and nerve tissue, and again talc was found to be an undesirable irritant.

Ross & Lubitz (1949) published 29 cases in which postoperative complications in wounds occurred, due entirely to talc implantation. Talc granulomata formed which resulted in fistulae, sinuses, tumours, non union in bones after open reduction, and in sinuses from bones after curetting them for Osteomyelites.

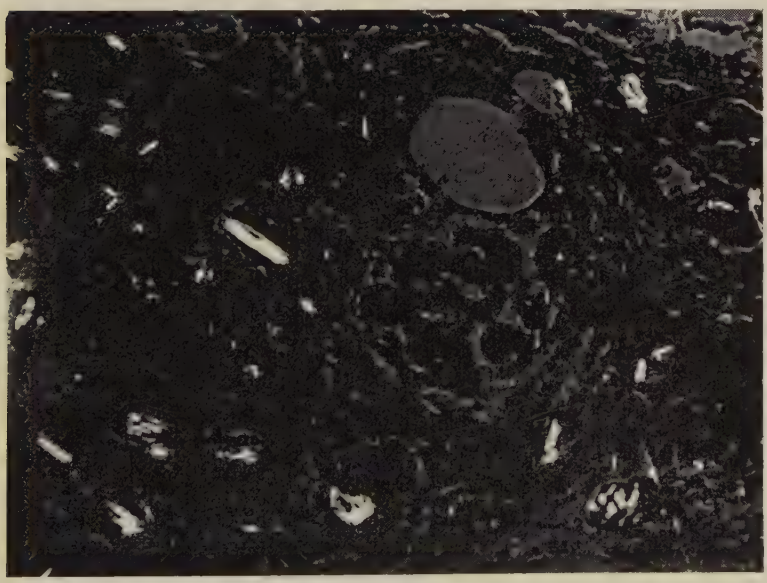
They describe 9 cases of sinuses in wounds after chest operations. These sisuses had to be excied. Eight cases of pilonidal sinus were recurrent due to talc powder implantation at the first operation. They emphasized the inadvisability of using talc as glove powder.

Baar (1953) reports a case of talc granuloma which simulated carcinoma. The woman aged 63, was found to have a mass in

Mr Baar's case of talc granuloma which simulated a carcinoma in the pelvis. By kind permission of Mr F. Baar, and the Editor, B. M. J. May 23, 1146. (1953).



This section shows granulomatous tissue, muscular hypertrophy, oedema and fibrosis of the submucosa and chronic inflammatory infiltration and fibrosis of the serosa.



The same section under polarized light ($\times$ 260), the talc particles appearing as birefringent crystals.

the Right Iliac Fossa which was hard and fixed. It suggested a fibroid as it was attached to the uterus. At Laparotomy the tumour was seen to originate from the sigmoid colon which was attached to the uterus. The diagnosis of carcinoma or diverticulitis was made. A transverse colostomy was done, and sixteen days later the abnormal part of the sigmoid was resected and an end to end anastomosis made as no secondaries were palpable. The patient was discharged after a month. Ten weeks later she was re-admitted for closure of the colostomy after which she made an uneventful recovery.

Section of the specimen showed inflammation of an unusual nature and the lesion was said to resemble Crohn's Disease.

The specimen was later sent to Prof. Newcomb who considered the condition chiefly due to talc granuloma. Small anisotropic particles were demonstrated. The patient's history varified that she had a cholecystectomy 7 years previously.

I. HEPARIN.

Chandy from Philadelphia (1950) did extensive work on rats using heparin to ascertain its effectiveness in the treatment of abdominal adhesions.

He wrote that many attemps have been made to prevent adhesion formation in the peritoneum on the principle of interfering with the blood-coagulation mechanism. This mechanism was assumed to be an important stage in adhesion formation.

Pope (1914) reported experiments on rats in which he used Sodium Citrate to lower the concentration of calcium ions. He hoped to prevent adhesions by interfering with coagulation. He reported favourable results by this method.

Sweet, Chaney and Willson (1915) and Kubota (1922) were unable to confirm this method after investigation.

A great deal of work was done later by Lehman and Boys (1940, 1941, 1942) who suggested the use of intraperitoneal heparin in the prevention of the formation and reformation of adhesions. They produced adhesions in dogs by a first operation and divided the adhesions at a second operation. Some served as controls, and others were treated with heparin.

In their experiments reformed adhesions were reduced from 1.57 times the number to 0.26 times the number divided at operation.

In another group, 26 animals used as controls formed adhesions, but only 1 of 10 animals formed adhesions if treated with heparin.

They reported 14 clinical cases in whom heparin was used. In this series one patient died of haemorrhage. No data on the other 13 cases were given as to the effectiveness of their therapy.

Chandy (1950) performed his experiments in rats and results obtained were at variance with those reported by Lehman and Boys who used dogs and rabbits. Chandy used albino rats of pure strain and standardized their nutrition. He used two types of trauma, chemical and mechanical.

The chemical trauma consisted of 0.05 cc of 3 % Sodium Hydroxide and was injected into the peritoneal cavity. In the control series of 30 animals all formed adhesions and one died.

The caecum was crushed at laparotomy to produce mechanical trauma, and all controls formed adhesions. (Subsequent experience indicated that mechanical injury such as this does not invariably form adhesions.)

They used 35 rats and heparin was injected intraperitoneally in varying amounts.

The table given below shows his dosage and results. Fatalaties due to haemorrhage increased when doses of heparin were increased.

Chandy summarized his results by reporting that heparin did not prevent adhesions in the rat under a variety of conditions, even though it prevented the coagulation of blood in the peritoneal cavity. This suggested to Chandy (1950) that the usual blood coagulation mechanism is not essential in the process of adhesion formation in rats.

J. CORTISONE.

The action of Cortisone on adhesions produced by talc suspension was determined by Odell, Key and Taylor (1951).

Their experimental study consisted of three series, and adult albino rats were used.

In Series I 40 animals were used.

21 of these were given three mg. Cortisone for 7 days before receiving talc.

19 animals were controls.

Dosage of Heparin and Results.

No of Rats	Procedure *	Results
5	NaOH 3 %, 0.05 cc. intraperitoneally Heparin, 0.05 cc. in 2 cc. sodium chloride solution ½ hr after	All had adhesions on the 4th day
5	NaOH 3 %, 0.05 cc. intraperitoneally Heparin, 0.05 cc. in 2 cc. sodium chloride solution ½ hr after Heparin, 0.05 cc. in 2 cc. sodium chloride solution 5 hr later	All had adhesions on the 3rd day
5	NaOH 3 %, 0.05 cc. intraperitoneally Heparin, 0.1 cc. in 10 cc. sodium chloride solution ½ hr after Heparin, 0.1 cc. in 10 cc. sodium chloride solution 5 hr later Heparin, 0.1 cc. in 10 cc. sodium chloride solution 10 hr later	One died of hemorrhage; 4 had adhesions on the 4th day
5	NaOH 3 %, 0.05 cc. intraperitoneally Heparin, 0.2 cc. ½ hr later Heparin, 0.2 cc. 10 hr later	Three died of hemorrhage; 2 had adhesions on the 4th day
5	NaOH 3 %, 0.05 cc. intraperitoneally Heparin, 0.2 cc. in 20 cc. sodium chloride solution ½ hr after	All had adhesions on the 1st day
5	NaOH 3 %, 0.05 cc. intraperitoneally Blood, 2 cc. with heparin 0.1 cc.	All had adhesions on the 4th day
2	Traumatized cecum at operation Heparin, 0.2 cc. in 10 cc. sodium chloride solution at time of operation Heparin, 0.2 cc. in 10 cc. sodium chloride solution 4 hr after	Both had adhesions on the 1st day
3	Traumatized cecum at operation Heparin, 0.2 cc. at time of operation Heparin, 0.2 cc. after 4 hr	Two died of hemorrhage; 1 had adhesions on the 4th day

On the seventh day 0.5 gm. of talc suspension containing 0.1 cc. India ink, was injected into all animals intraperitoneally.

The 21 animals received 3 mg. cortisone daily.

The animals were sacrificed at 1, 2, 3, 4, 7, 14, 21, and 28 days for post mortem and histological study.

In Series II 32 animals were used. A similar 0.5 gm. talc injection was given into the peritoneal cavity. Sixteen rats received

* 1 cc. heparin = 10 mg.

By kind permission of Dr. J. Chandy, (1950) Arch. Surg. 60, P. 1151. (The Am. Med. Ass., 535 N. Dearborn St., Chicago, 10.)

3 mg. cortisone at the time of injection and this dose was repeated daily until they were sacrificed. Overdoses of ether were given after 1, 2, 3, 4, 7, 14, and 28 days, and studies made.

In Series III 24 animals were used and treated as in series I, but cortisone was injected for only 5 days instead of 7 days before talc was injected. They were killed on similar days as Series II.

Results. All the animals became ill with diarrhoea after the talc injections.

In the control animals diarrhoea lasted for 2 to 3 days and two died.

In treated animals diarrhoea lasted for one day and none died.

1 to 4 days. Treated animals showed dispersing of the talc and no adhesions. In control animals the talc was localised, surrounded by fibrin and adhesions commenced. Intestines were already matted by adhesions after 2 days, the peritoneal fluid was sanguinous and proximal bowel loops were distended.

7 days. The free fluid was almost absorbed and India ink was disperced. Little evidence of adhesions was found. Controls continued to show localization of in and talc. A mass adherent to intestines, omentum, liver, spleen and diaphragm was seen. In an attempt to separate adhesions the bowel was torn.

14 days. In treated animals no peritoneal fluid was found. Visceral peritoneum was smooth and glistening. Omentum was free and very few adhesions seen.

Control animals had no free fluid, but adhesions were dense and matted the abdominal contents. Talc granulomata were found on the liver in several cases.

21—28 days. Similar results were seen and in treated animals very few adhesions.

In Series III talc injections were preceeded by only 5 Cortisone injections. The results were the same as Part I.

In Series II 4 animals died of obstruction due to adhesions from talc. Three were control animals and one of the treated animals also died from adhesions and obstruction.

Cortisone treatement was started on the same day as the talc injection in this series, and was given daily until the animal was killed.

1—4 days. Control and treated animals behaved the same for

4 days. Bloody fluid was noted on the 4th day. Bowel loops were distended, and matting of loops was seen due to early adhesions.

7 days. Matting of abdominal contents still seen and adhesions were difficult to separate. In treated animals ¼ to ⅛ the amount of matting was encountered.

14 days. Thick adhesions caused abdominal contents to form an adherent mass. More delicate adhesions were found in treated animals.

14, 21 and 28 days. The same results were noted.

Odell, Key & Taylor (1951) state in their discussion that Cortisone disperses the talc and keeps it in suspension in the peritoneal exudate, and it acts as a spreading factor not unlike hyaluronidase.

They thought that Cortisone acts by a combination of factors:

1. The prevention of coagulation of fibrin and exudate.
2. It probably increases intestinal mobility.
3. It inhibits fibroblastic response to injury.

They concluded that Cortisone greatly reduced adhesions in rats when given 5—7 days prior to trauma. They recommended its use in selected patients in pre- and postoperative treatment. They suggested 100 mg. by mouth for 2 days before and 7 days after operation.

Cortisone and Corticotrophin (A. C. T. H.).

Scheinberg and Saltzstein (1951) made an experimental study of the effect of Cortisone and Corticotrophin (A. C. T. H.) on abdominal adhesions.

Their procedure was to sprinkle 0.25 gm. of talc powder evenly over the serosal surface of the small intestine and its mesentery. They used 30 mongrel dogs.

Ten animals were used as controls.

Ten received 10 mg. Cortisone intramuscularly twice daily for two weeks.

Ten received 5 mg. of A. C. T. H. twice daily.

Effective doses were determined from Eosinophile counts. Animals that showed a 50 % drop in Eosinophils or more were taken to be receiving effective doses.

They were killed from 2 to 6 weeks after operation as demonstrated below:

Time killed after operation	Controls	Treated with Cortisone	Treated with A. C. T. H.
3 weeks	2	5	3
4 weeks	4	5	4
6 weeks	4	0	3

The Results: Control animals all showed the usual talc results: Adherent masses, bound up mesentery, and bowel adherent to liver and anterior abdominal wall.

All Cortisone-treated animals showed normal thin serosa, loops were easy to deliver through the wound and no adhesions to liver or abdominal wall were seen.

Adhesions were present, but they were thin and fragile, easily separated by the fingers. Bowel loops were stuck together in some places but the density of adhesions was much reduced.

Animals treated with A. C. T. H. showed the same results.

Adhesions were counted, to obtain numerical comparisons as shown below:

One if they were 1 cm. or less in length.
Two „ „ „ 2 „ „ „ „ „
Three „ „ „ 3 „ „ „ „ „
Four „ „ „ 4 „ „ „ „ „ regardless of width.

Sharp angulations, or hairpin turns of the bowel loops were also tabulated.

From estimation in this way dogs treated with cortisone and A. C. T. H. showed 75 % less and 60 % less hairpin turns than controls.

Their illustrations below summarize results obtained by Scheinberg and Saltzstein (1951).

Adhesions and hairpin turns were 15.0 and 3.2 respectively in treated dogs.
„ „ „ „ „ 45.3 and 8.3 respectively in controls.

They were faced with four questions:

1. What dosage would prevent adhesions?
2. For how long would treatment be necessary to prevent adhesions?
3. When do adhesions first appear?
4. Would treatment delay wound healing?

They used rats experimentally to determine these unknowns, but suggested that more work will have to be done to answer the questions definitely.

Experiments. Twenty rats were used and received 10 % Talcum Saline suspension by injection into the peritoneal cavity. Cortisone 2 mg. daily was then given for 13 days. Ten controls were kept.

In controls a total of 55 adhesions and 26 hairpin turns formed. In treated animals 2 adhesions and No hairpin turns formed.

1. *Dosage:*

   (a) Six rats were given 0.5 mg. Cortisone daily for 13 days

   (b) „ „ „ „ 1.0 „ „ „ „ „ „

   (c) „ „ „ „ 2.0 „ „ „ „ „ „

   At obduction the number of adhesions were:

   (a) 28.

   (b) 5.

   (c) 2.

   This determined that 2 mg. was the necessary dose.

2. *Duration of treatment required:*

   After the talc was given, 6 rats were given 2 mg. Cortisone for 7 days. They were killed on the 7th day and none formed adhesions.

   Six rats were given 2 mg. for 7 days, and were killed on the 14th day. Three animals formed adhesions. This showed that 7 days treatment is insuffisient treatment with Cortisone.

3. *When do adhesions first appear?*

Six series of 6 (i. e. 36 rats) were given talc suspension intraperitoneally.
In each series three were kept as controls, and three were given 2 mg. Cortisone daily.
Three controls and three treated animals were killed at 3, 4, 6, 8, 10 and 12 day intervals after the talc injection.
On the third day controls showed agglutination of bowels and hairpin turns.
On the 6th day definite adhesions were found. In treated animals no adhesions were seen until the 8th day, and then they were minimal.
After the 10th day there were no adhesions apparent in treated animals.

4. *Delay in Wound healing.*

Wounds were produced by making skin defects in the abdominal walls of 28 rats. A cork borer was turned through the skin and a circular defect excised. Animals were divided into groups of four each as follows:
Group A served as controls. Groups B, C, D, E & F were given 0.5, 1, 2, 3, 4 and 5 mg. Cortisone daily.
All animals were examined on the 12th day. In Group A, B, C and D healing was complete. In Groups E, F and G, given 3 mg. and over daily, there were unhealed areas measuring up to 1 cm. in all animals.

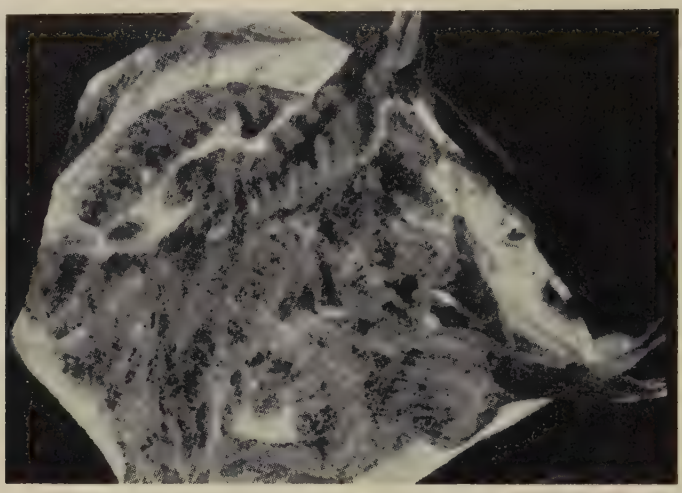
Scheinberg and Saltzstein (1951) concluded that in white rats injections of 2 mg. Cortisone daily will prevent adhesions without delay in healing, but 3 mg. and over for 12 days will delay healing.

Comment. Sprague (1950) and others have shown that in man large doses of Cortisone (200 mg. Cortisone or 105 mg. A. C. T. H.) result in loss of nitrogen from the body, increase of Catabolism of Protein, increase excretion of uric acid, creatinuria, and amongst others wound healing is delayed.

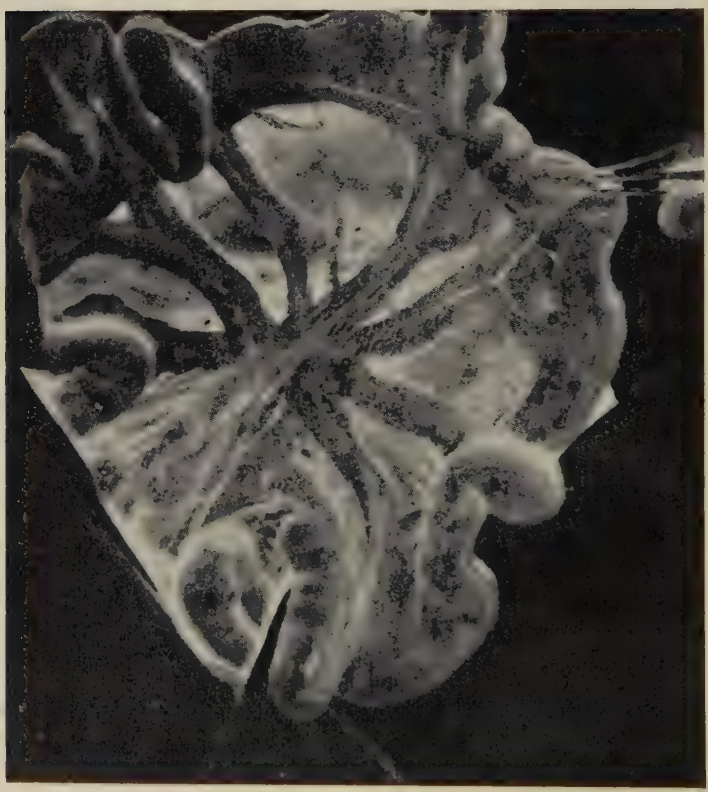
Ragan et al. (1950) noted delay in the healing of incised wounds in patients treated with Cortisone for other illnesses e. g. Rheuma-

The animals were killed from two to six weeks after operation, as follows:

Dry Killed	Controls	Treated with Cortisone	Treated with Cortico-trophii
After 2 wk	2	5	3
After 4 wk	4	5	4
After 6 wk	4	0	3

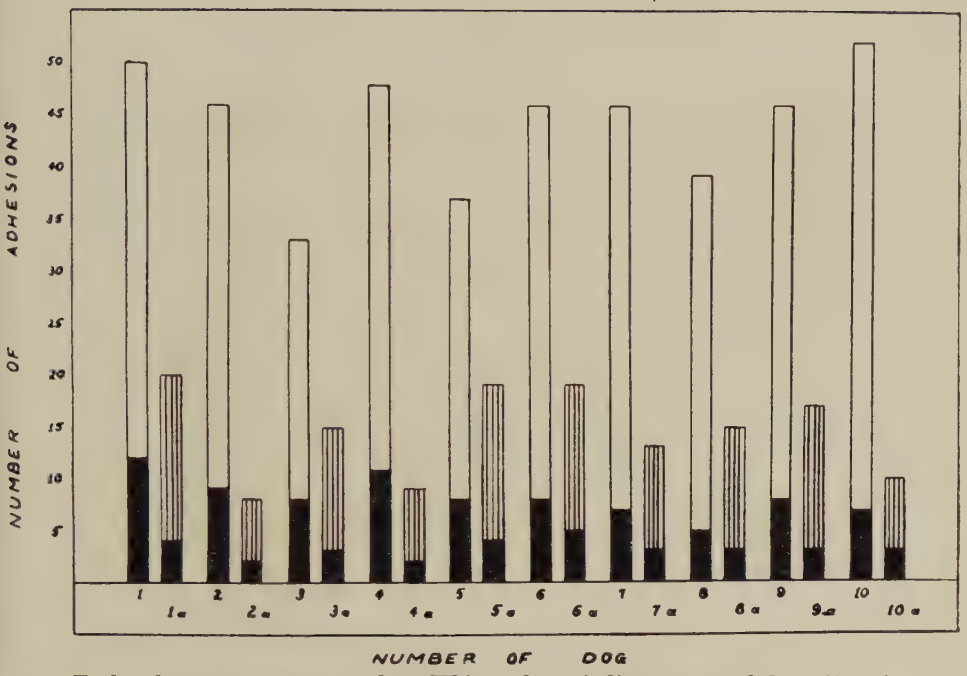


Control dog, killed 14 days after application of talcum powder. Note dense mass of adherent loops.

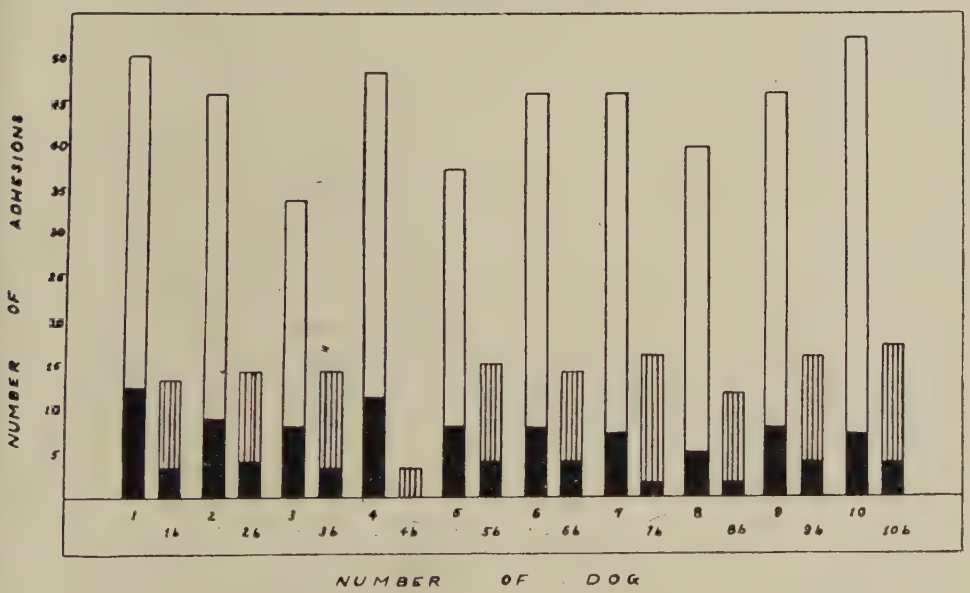


Dog killed on 14th day after administration of 10 mg. of cortisone twice daily. Note scarcity of adhesions, with the smooth, thin, glistening mesentery.

By kind permission of Drs. S. R. Scheinberg & H. C. Saltzstein, (1951) Arch. Surg. 63, p. 413.
(Amer. Med. Ass., 535 N. Dearborn St., Chicago, 10).



Each column represents one dog. White column indicates control dogs (1 etc.) and striped column, dogs treated with cortisone (1d etc.). Solid portion denotes number of hairpin turns.



Each column represents one dog. White column indicates control dogs (1 etc.) and striped column, dogs treated with corticotrophin (1b etc.). Solid portion denotes number of hairpin turns.

By kind permission of Drs. S. R. Scheinberg & H. C. Saltzstein (1951) Arch. Surg. 63, p. 413.
(Amer. Med. Ass., 535 N. Dearborn St., Chicago, 10).

toid Arthritis. There was also depression of the growth of granulations in open wounds.

Rabbits were then used experimentally. Some were treated and others left as controls.

After five days control wounds were covered with granulations. Histologically these wounds showed profuse growth of fibroblasts, blood vessels and ground substance.

In the animals treated with Cortisone no new granulation tissue appeared, the blood vessels were exposed, and microscopic examination proved a marked suppression of all elements of connective tissue which are normally found in healing wounds.

Spain (1950) and others found the same suppression of fibroblastic reaction in wound healing with Cortisone treatment.

According to Scheinberg & Saltzstein (1951) it is necessary to give Cortisone for at least 10—14 days to prevent adhesions.

In experimental animals granulation tissue was found within one hour. Cortisone therapy should be commenced on the day of injury and continued long enough to prevent fibroblastic proliferation. They found 10—14 days sufficient.

They explain the shorter duration of heparin treatment (3 days) by its different mode of action. Heparin prevents the formation of fibrin, and Cortisone delays formation of granulation tissue. i. e. fibroblasts, blood vesels and ground substance.

The authors concluded that Cortisone treatment reduces the formation of intra-abdominal adhesions. In proper doses it did not delay healing. Daily injections for 10—14 days seemed to be necessary to prevent adhesions.

K. HYALURONIDASE IN THE PREVENTION OF INTESTINAL ADHESIONS.

John Thomas, Chandy et al. (1950) investigated the influence of hyaluronidase on the formation of intraperitoneal adhesions. They extended the experiments performed by Chandy & Rhoads in 1946 and which resulted in reduction of adhesions when hyaluronidase was applied locally. It was applied after crush injury to the caecum in rats.

Thus Thomas, Chandy et al. (1950) used 110 rats to determine the inhibitive power of hyaluronidase. They used different types

of trauma to the caecum and treated with more than one preparation of hyaluronidase as follows:

No. Treated	Make of Hyaluronidase	Dosage	Trauma
44	Hyaluronidase (Schering)	5 % sol.	Allis tissue forceps
19	Wydase (Wyeth)	1250 T. R. U.	Payr clamp
47	Alidase (Searle)	1250 V. R. U.	Kelly Haemostat

T. R. U. Turbidity reducing units.
V. R. U. Viscosity reducing units.

Results. Adhesions developed in 76 % treated animals and in 89 % controls. These authors concluded that hyaluronidase is ineffective in preventing adhesions, and could not support their first conslusion.

Conolly & Richards (1951) of San Francisco did further experiments using this enzyme. They were encouraged not only by the rapid diffusion it promoted into the tissues, but also by its spreading factor which seemed similar to that described by Duran-Reynals in 1942.

Schwartzman et al. (1948) studied its action and described the ease with which fluids were absorbed when hyaluronidase was added.

Its spreading effect when used in conjunction with local and infiltration anaesthesia was established by Kirby et al. (1949).

Rutenburg, Seligman & Fine (1949) combined hyaluronidase with emulsified fat, while studying the absorption of fat from the peritoneal cavity in dogs. They observed that animals which received intraperitoneal fat alone formed many adhesions. Those injected with both fat and hyaluronidase formed no adhesions.

Conolly & Richards (1951) were thus inspired by this observation to use it in the prevention of adhesions.

Experiments. They performed thirty operations in 14 adult dogs which weighed 7 to 10 kg. Talc was used to produce adhesions, "the amount ordinarily used by a surgeon before donning his gloves" was used by them in the production of massive abdominal adhesions. (The weight of talc is not stated by them.)

By a small laparotomy the talc was spread over the bowel loops.

In the first few experiments they added small amounts of hyaluronidase to the talc at laparotomy. With this addition they found that no adhesions occurred.

They then produced adhesions with talc alone and later studied the effect of hyaluronidase. Twenty eight experiments on 14 dogs were performed. Talc injury was first performed and later the adhesions separated manually.

In 7 dogs no treatment was given after separating adhesions. In the other 7 animals hyaluronidase was given as follows:

In 2 animals (2 ampules) 1000 units were given in 10 cc. Isotonic Saline.

In 5 animals (4 ampules) 2000 units were given in 10 cc. Isotonic Saline in one application at operation.

In these 7 animals, bowel and gastric anastomoses were made to study its possible influence on healing.

Results. In the controls all the adhesions reformed.

In the 2 dogs where 1000 units were used some adhesions reformed, but fewer than were present at lysis.

In the 5 dogs where 2000 units were used there were no adhesions.

Microscopic sections in treated animals of the anastomosed areas showed no gross retardation by comparison with controls.

In their Discussion Conolly & Richards (1951) state that the apparant action of hyaluronidase in preventing adhesions is not known. They think that it probably antagonises the hyaluronic acid secreted by fibroblasts, and that a high dosage in treatment is imperative.

They thought that Thomas et al. (1950) were unsuccessful in their experiments due to insufficient dosage.

Hyaluronidase was instilled in one application into 14 clinical cases after obstruction due to adhesions. Twelve cases had no further clinical obstructions over a period of 3 to 14 months. The other two cases obstructed 7 and 30 days after operation. They thought that a higher dosage of enzyme should have been used. Their dosage was 6000 units, Searle, in 20 cc. isotonic saline. To obtain better results they suggested a dosage of 10.000 to 12.500 units, in the average size patient.

They also advised an initial intradermal testdose before treatment.

CHAPTER IX.

AUTHOR'S OWN WORK AND FINDINGS.

In the previous chapters of this thesis a review is given of the work done on this subject and all the facts known about adhesions from the earliest times to the present day.

There seems to be little doubt that up to the present the true principle of the treatment of adhesions has not yet been established. More obvious is the fact that most work done in the past has been experimental. This shows us that no method which establishes a principle, or particular remedy has yet been generally accepted by surgeons.

It is therefore impossible in this work to produce clinical statistics. To do this would require many years of observation, and an equal number of control cases would have to be recorded.

An attempt is therefore made to establish the principle of treatment experimentally, which entails the greatest part of this study.

From the pathology in this work, and from more important studies in the past, it is obvious that every effort must be made to prevent fibroblastic invasion of the exudate from the traumatized area.

Ten minutes after injury to the peritoneum there is an exudate of serum and fibrin.

After two hours fibrin agglutinates the denuded serosa to some other peritoneal surface. In 18 to 24 hours fibrinous bands and even new blood and lymph vessels are found. Fibroblastic proliferation commences from the third to the fifth day, and this may continue until fibrin has been completely replaced by connective tissue. Hertzler (1921).

To prevent the fibroblastic stage it is necessary to start treatment immediately after trauma and to give treatment regularly if the fibroblast stage is to be prevented.

If the exudate is allowed to remain, to coagulate, and fibrin adheres it to another surface, the fibroblast is sure to follow.

Throughout the study of adhesions the individual variations in the formation of adhesions are seen. There are variations in formation and in response to treatment which one cannot account for in theory or expectation. This fact has been stressed by many authors on the subject of adhesions, and has been explained by calling it an individual diathesis.

In the prevention of adhesions we must remember that the fibroblast appears from the third to the fifth day. In this work the minimum period required to remove the exudate, fibrin, and fibroblastic reaction has been fixed at six days. If there is repeated exudation of serum and fibrin after the first exudate is removed, but removal is repeated for six days, the serosa heals without becoming adherent to another surface.

Traumatic injury in animals, done in this study, consisted of injury to the serosa and the underlying tissue to make sure of the formation of adhesions. It will be seen that the healing of serosa is probably achieved by the mononuclear leucocyte, and the underlying tissue if injured, by the fibroblast.

It seems logical to prevent adhesion formation through a combination of methods by:

(a) Frequently diluting the exudate, and starting immediately after trauma to the peritoneum.

(b) Adding a spreading factor daily for 6 days to the dilutant to hasten absorption of the exudate.

(c) Adding an enzyme to the dilutant for 6 days in the hope of dissolving fibrinous adhesions.

Hyaluronidase, prepared from testicular extract, conforms to our requirements in treatment. It will be shown later that hyaluronidase prepared from bacterial arigin is of little value or would probably have to be used in greater strength.

The richest sources of hyaluronidase are testicular extract, staphylococci, streptococci groups A and C, pneumococci, and Clostridium Welchii.

Two types of hyaluronidase are prepared; one from testicular extract, and the other from bacteria.

It is necessary to know a little more about this preparation and the history of its discovery.

Duran-Reynals in 1929 reported his second paper. In a previous paper he found that when an agent of chicken tumor I was brought into contact with finely ground muscle of susceptible animals it was bound, so that both the supernatant fluid and muscle tissue became inactive when injected into chickens.

In his second study he undertook to determine whether a filter-passing virus (such as vaccine virus) could be demonstrated to have a similar effect.

From extensive work he found that brain and testicle tissues from immune rabbits, when brought in contact with Levaditi or Noguchi strains of vaccine virus, will fix or inactivate the virus.

Extracts of normal testis from susceptable animals enhanced to an extra-ordinary degree the infectivity of the neuro- and dermal strains of the virus.

Kidney extract had a definite enhancing power on the Noguchi virus when injected into skin or testicle.

Duran-Reynals (1929) also found that enhanced lesions resulted when the virus was injected into an area, as long as 3 days after the area had been injected with testicle extract.

Rabbits with enhanced lesions showed general symptoms, and about 20 % died with generalized vaccinia.

This was the initial demonstration of the "Spreading Factor."

Meyer & Palmer (1934) tried to split the mucoid substance contained in vitreous humour, into its polysaccharide and protein components.

After lengthy chemical processes on lots of 100 calves eyes from the abatoir, they separated out a polysaccharide acid which they termed "hyaluronic acid."

It has the apparent equivalent weight of about 450, and its dissociation constant was determined as 4.58×10^{-5} at 32° C.

Chain & Duthie (1940) proved that:

1. An enzyme was present in all sources of spreading factor investigated, and that spread in the skin has never been observed in solutions not containing the enzyme.

2. A quantitative correlation exists between the enzyme and spreading activity.

The Principle of treatment of Adhesions.

Frequently **diluting** the exudate starting immediately after trauma.

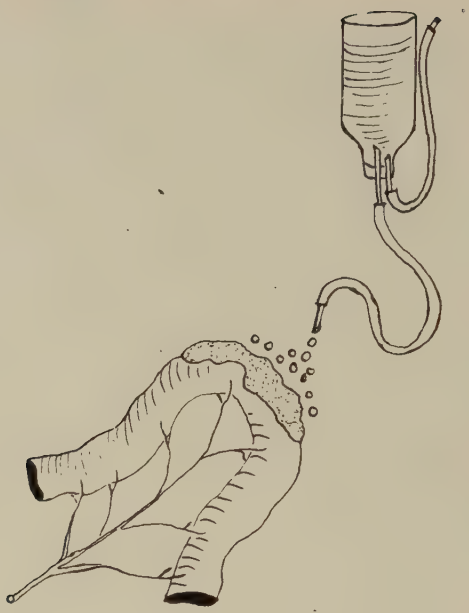


Fig. (a)

Adding **spreading factor** for 6 days to the dilutant which hastens absorption of the exudate.

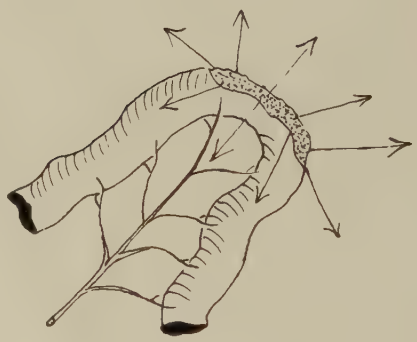


Fig. (b)

Adding an **enzyme** for 6 days which dissolves fibrinous adhesions.

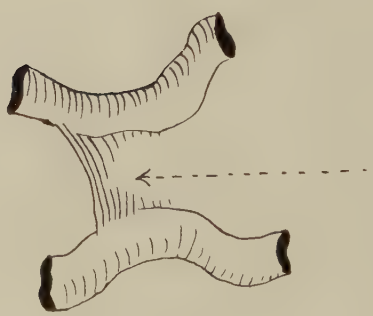


Fig. (c)

3. A mucin like substance had been isolated from the skin with properties similar to vitreous humour and synovial fluid, and it acted in the same way.

They proved three ways of testing the activity of hyaluronidase, most important being the rate of decrease in viscosity of hyaluronic acid by the enzyme.

They found that the substance hyaluronidase showed no loss of activity when incubated for 12 hours at 37° C. when tested between P. H. 4.6 and 9.

The enzyme was found to be present in the testis.

The mucinous substance that occurs in sexual skin of monkeys during the oestrous phase is acted on by hyaluronidase and is thus closely related to hyaluronic acid according to their findings.

To summarize the findings of these authors they found:

1. That this factor was an enzyme which they termed hyaluronidase.
2. It depolymerizes hyaluronic acid which contains gluco-uronic acid and N-acetyl-glucosamide.
3. This was isolated by Meyer & Palmer from vitreous humour. synovial fluid, umbilical cord, tissues and fluids from certain tumours and pig skin.

Hyaluronic acid is now regarded as "tissue cement" or "ground substance" of tissue spaces. It forms viscous solutions but hyaluronidase reduces the viscosity of this thick fluid to that of water. This accounts for the *spreading phenomenon* produced by this enzyme on some animal tissues.

It is prepared as a dry powder, sterile and free from anaphylactogens and toxicity.

The Benger product used in this work is made in ampules containing 1.0 mg. of the powder, and an activity of 1000 units is assigned to it.

According to American products (Wyeth Incorp. Philadelphia) the spreading factor has its richest sources in testicular extract, Groups A & C Strepococci, Saphylococci, Pneumococci, Clostidium Weilshii, and the venom of poisonous snakes and insects.

Bacterial invasiveness associated with infections and rapid

development of symptoms following poisonous snake and insect bites are due in part to the spreading effect of hyaluronidase. (Duran-Reynals 1938.)

The following uses have been attributed to hyaluronidase:

1. In subcutaneus transfusions to supply fluid in paediatrics.
2. To be added when large injections are given.
3. Added to local anaesthesia in surgery to spread the effect.
4. In pleural and peritoneal paracentesis.
5. Hydrocephalus.
6. Arthritis, sprains, and bursitis.
7. In Haemarthrosis, and reduction of haematomas.
8. Oedema of a limb.
9. In reduction of fractures with local anaesthesia.
10. It is said to have aided cases of sterility.

Dr. Marie Stoppelman (1949) of the paediatric clinic in Amsterdam gives a review of the literature on this enzyme and its effect on the permeability of tissues.

Duran-Reynals (1938) found that the spreading factor was present in snake venom, and extracts of pyogenic staphylococci (Duran-Reynals 1933) and it was found in haemolytic streptococci by McClean (1936).

In the combination of bacterial suspensions with testicular extract the results after injection depended on the concentration and virulence of the bacterial element.

Adding testicular extract to a virulent emulsion which is well diluted resulted in a milder infection.

The same result is obtained by adding testicular extract to a concentrated suspension of avirulent bacteria.

Stoppelman (1949) considers hyaluronidase one of the important factors that influence the permeability of tissues, and inter alia, the spreading invasiveness of bacteria.

The hyaluronidase associated with spermatozoa would hasten the fertilization of the ovum by making the layer surrounding the ovum more permeable. It has thus been claimed to have an influence on sterility. (Ausin 1948.)

The effectiveness of hyaluronidase has been tested for its hy-

podermoclysis. Two drips were used, one in each leg subcutaneously. The one in which hyaluronidase was previously injected, absorbed the fluid much more rapidly. No toxic symptoms were noted.

Twenty four hours after injection the preparation was still found to be effective, after which its influence could not be detected. (This finding its of utmost importance in the treatment of intraperitoneal adhesions. We can deduce from this statement that hyaluronidase treatment should be given very punctually on the same hour at 24 hour intervals if the maximum effect is desired.)

Stoppelman (1949) mentions that although patients may suffer from diseases like rheumatic fever which promote anti-hyaluronidase in the serum, this has no relation to the effect of hyaluronidase on tissue permeability.

From this literature of hyaluronidase we can see that it is the product of choice in the treatment of adhesions because:

(a) It can be conveniently injected intraperitoneally at 24 hour intervals, and it tends to reduce the viscosity of some fluids. If it has even a mild dissolving action on an exudate it would be a tremendous advantage in treatment.

(b) It is an enzyme which may be diluted with many types of fluid without losing its effect on tissue permeability.

(c) It hastens absorption by its spreading factor action and so may prevent stagnation and progress of a traumatic exudate (the earliest stage of an adhesion).

(d) It is possible that its enzyme effect could cause dissolution of a fibrinous adhesion.

(e) Its action on the fibroblast is not yet known, but results in treatment suggest that it may have a retarding influence on fibroblastic reaction.

Besides the above mentioned reasons for the use of hyaluronidase, one feels that it is a product which is extracted from animal tissues, and it seems to have no side effects. In action it reminds us of the proteolytic enzyme found in the peritoneal fluid during the leucocytic stage of the exudate after trauma.

The exudate shows leucocytic infiltration 18 hours after trauma

so that we may expect the proteolytic enzyme to follow soon afterwards. In the battle against adhesions we have the advantage of adding enzyme immediately after trauma, in much higher concentration than the natural proteolytic enzyme, and flush the peritoneal fluid with it every 24 hours to ensure the maximum chance of prevention.

Experimental work.

In the experimental study of adhesions rabbits were chosen, because they are of fair size, and give one a fair sized small intestine to carry out investigation.

Experienced laboratory technicians consider them sensitive animals which die easily. They are undoubtedly sensitive to anaesthetics and must be kept warm afterwards or pneumonia frequently follows. General anaesthesia was employed. Thiopentone well diluted to 2½ or even 1 % was given intravenously into the ear in all procedures which required handling of the bowel.

For the production of adhesions, several types of trauma were tested, but for the true action of hyaluronidase mechanical and talc trauma were employed. Mostly mechanical trauma was relied upon, because this is the normal way in which the bowel is injured during operative procedures or in lysis of adhesions. The serosa of the rabbit is extreemly thin, and in carrying out mechanical trauma the underlying tissue is invariably injured during the process, and perforation by trauma occurred in 25 % of animals.

If tissues underlying the serosa are injured during mechanical trauma there is a much greater tendency to adhesion formation. This fact has been stressed by other authors mentioned above in the literature on adhesions.

Method of Mechanical Trauma.

A midline abdominal incision was made under general anaesthesia, and a loop of ileum delivered through the wound. About 10 cms. of continuous serosa over the loop was scraped off by means of a fine toothed instrument specially made for the purpose (fig. 1). The trauma was made on one side of the bowel, and

enough to cause some bleeding so that when the loop was returned into the abdomen, the injured side would tend to agglutinate to itself by approximation or to a neighbouring surface.

A loop of bowel in a control animal which has become completely adherent to itself after 14 days is shown in fig. 2.

The table below indicates the numbers of animals used and the type of investigation done.

Altogether 94 rabbits were used, 94 operations were done and over 300 injections were given.

No of Rabbits	Type of Trauma	Type of Investigation	No of Operations
6	Mechanical	Test group 4 Treated with H	
		2 Controls	6
18	Mechanical	15 Treated with H from bacterial origin	
		3 Controls	18
12	Mechanical	Treated with Testicular H	12
10	Talc	Treated with Testicular H	10
5	Talc	Controls	—
5	Tr. Iodine	Effects studied	5
10	Mechanical	To produce adhesions	10
Same Rabbits	—	Lysis of adhesions and treatment with H	10
5	Blood into Peritoneum	Effects studied	5
5	K 285 (new glove powder)	Effects studied	—
7	Mechanical	Pathological studies	7
3	—	Intestinal anastomoses	3
6	Sepsis Induced	Study of Sepsis + H	6
2	Dry swab injury	Study result	2
Totals 94		104 Investigations	94

H = Hyaluronidase.

TEST GROUP I.

The experiments on this group of 6 animals were done in South Africa. All the experiments that followed were done in Prof. Dr. W. F. Suermond's Department at the University of Leiden Hospital.

In this group the intestines of 6 animals were traumatized. Two served as controls and four were treated for 6 days with 1500 units of Hyaluronidase (Benger) daily. The smallest catheter was left in the peritoneum and stitched to the skin when the wound was closed. The outer end of the catheter was closed off with a clip so that intraperitoneal injections could be given through the tube. (See fig. 4.) Hyalorunidase was given dissolved in 5 cc. physiological saline. It was injected through the tube at body temperature or slightly above, and this is important as cold solutions cause pain and discomfort in the peritoneal cavity.

Results. Both controls formed adhesions and 3 treated animals were completely free from adhesions. The 4th animal showed dense adhesions from the small intestine to the site where the tube was removed on the 6th day.

		No that formed adhesions	No free of Adhesion
No. Treated	4	1	3
No. of Controls	2	2	0

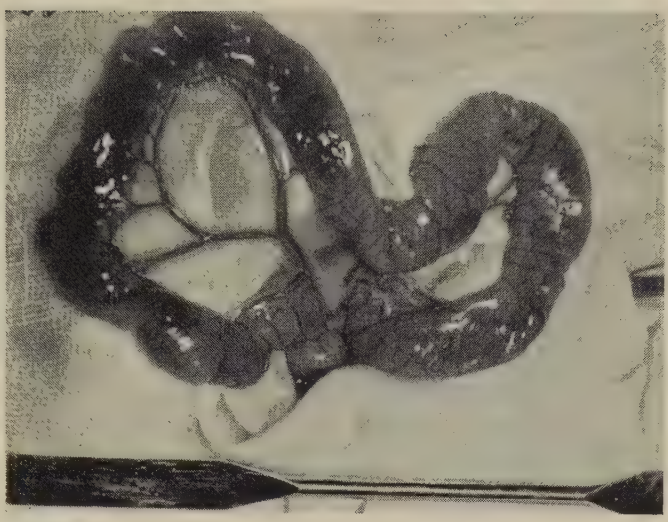
Note: Special thanks is due to Dr Daniel Joubert of Wellington, South Africa, whose laboratory experience gained in Holland, made the first experiments possible.

GROUP 2.

Mechanical Trauma and treatment with Hyaluronidase prepared from a Bacterial Origin.

Eighteen animals were used. A loop of intestine was traumatized in each animal under general anaesthesia. The instrument made for the purpose was used, and accidental perforation occurred in 4 animals. The smallest catheter was again stitched in situ. Two ampules containing 10 units of hyaluronidase in 5 cc

Mechanical Trauma.



A traumatized loop of small intestine and the instrument used to remove serosa and some underlying tissue.

Fig. 1.

The same loop 14 days after trauma.
The loop becomes firmly adherent if no treatment is given.

Fig. 2.

A similar loop from an animal treated for 6 days by intraperitoneal hyaluronidase (14 days after trauma).
There are no adhesions.

Fig. 3.

physiological saline at body temperature were injected immediately after operation, and again at 24 hour intervals.

Three animals served as controls, and although the catheter was also stitched into the peritoneum, no injections were given.

Two of the 15 animals under treatment died, one on the 2nd and ane on the 3rd day after operation. Obduction revealed that both died of acute obstruction following excessive trauma. Of the 13 that remained, 5 were injected daily for 3 days and 8 were injected dailly for 6 days through the tiny catheter. The animals were sacrificed after 2 weeks.

Results. In tabulating the results it has been found necessary to distinguish between adhesions of intestinal loops due to trauma, and the adhesions which formed at the site of the abdominal wound especially where the catheter was removed.

		Intestinal Adhesions		Adhesions to Abdominal wound	
	Number	No that formed adhesions	No free	No that formed adhesions	No free
Controls	3	3	0	0	3
Died	2	2	0	0	2
Treated 3 days	5	4	1	1	4
Treated 6 days	8	7	1	2	6
Treated Totals	15	13	2	3	12

In this group we see that 13 out of 15 treated animals formed adhesions in the intestines. The first animal that died had two injections and the second three injections. Both showed adhesions, and they were counted with treated cases. To the abdominal wound 3 out of 15 animals formed adhesions.

The excessively poor results in this group teach us that:

1. Hyaluronidase prepared from bacterial origin is useless in the treatment of adhesions.
2. That even the smallest catheter stitched into the peritoneum causes foreign body reaction in 20 % of the animals and should never be employed.

Hyaluronidase is not standardized internationally. Each firm has its own method of standardization, and the number of units

attributed to an ampule is an arbitrary figure added by the firm's laboratories. From extensive interviews this unfortunately is the conclusion we must accept, and also remember when giving treatment with hyaluronidase. An ampule made by each firm, on investigation, is more or less the strength required to hasten absorption of 500—1000 cubic centimetres of fluid when given subcutaneously. It is therefore important to have a sound knowledge of the preparation used, as insufficient dosage intraperitoneally will lead to failure.

Note: Professor Dr J. W. Duyff and his staff, of the Department of Physiology, University of Leiden, rendered assistance in specialized methods of preparing and anaesthetising the experimental animals.

Note: All experiments were carried out in an operating theatre and laboratory specially equipped for animals. These rooms, as well as staff, were made available by Professor Dr W. F. Suermondt, in his department.

GROUP 3.

In this group 22 animals were used and 22 laparotomies were performed. Twelve animals were traumatized mechanically as before, and again 4 cases were accidentally perforated.

The perforations are repaired by simple ligature in rabbits.

It was attempted to keep the trauma up to the same standard, and twelve centimetres of bowel was scraped. (See fig. 1.)

The other 10 animals were traumatized by spreading 100 mg. of sterilised talc powder (used for surgical gloves) over the loops of the small intestine.

No catheter was stitched into the peritoneum but the wound closed by an everting continuous stitch.

Two ampules of hyaluronidase (Benger) 2000 units in 5 cc. saline were injected intraperitoneally daily for 6 days in all animals. This hyaluronidase is prepared from bovine testis. (This information was obtained by personal communication.)

The saline used as solvent was heated up to 37°—40° C. by immersing the vacolitre into warm water. A water thermometer

Foreign Body reaction.

A small catheter produces adhesions in spite of curative treatment.

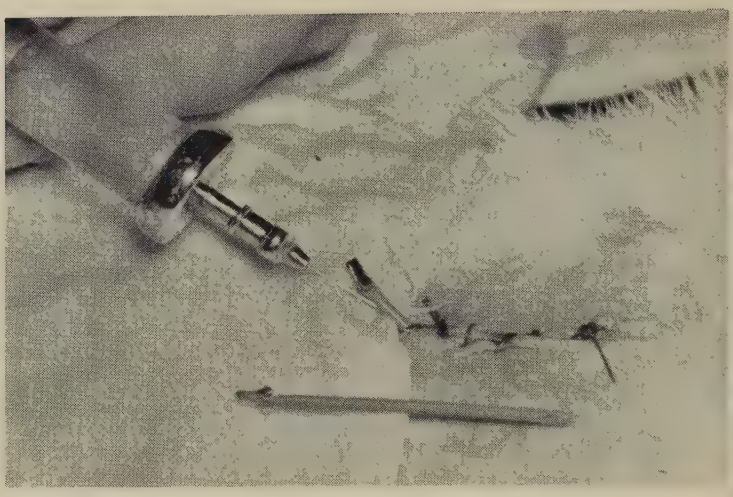


Fig. 4.

80 % of animals form no adhesions if catheter is left in for 3 to 6 days.

Fig. 5.

20 % of experimental animals form adhesions to the tube.

Fig. 6.

was used regularly as a check, and this is most important in intraperitoneal injections.

The animals were all sacrificed on the 14th day after operation.

Results. No adhesions formed in any of the intestines of the 22 animals.

From the abdominal wound one thin band was seen in one of the twelve traumatized animals. In the talc injured animals all 10 animals showed concentration of the talc at the abdominal scar, and 4 out of the 10 animals showed adhesions in this position.

Acting somewhat like the omentum (see fig. 6), talc seems to be attracted to the wound by electric potential. The irritating power of talc is doubled when applied to an injured area of peritoneum. The most remarkable fact is that none of the 10 intra-abdominal surfaces of the wounds had healed after 14 days. A forceps could be pushed through the thickness of the abdominal wall with ease where the talc was concentrated over the peritoneal surface. The delay in healing caused by talc has been insufficiently appreciated in the past. Over the small intestine we must acknowledge 100 % prevention of adhesions with hyaluronidase prepared from bovine testis.

The fact that one thin adhesion still occurred in one animal on the peritoneal surface of the abdominal scar, is sufficient evidence to show that 6 days treatment is the minimum period of treatment to be given.

Results after treatment with Hyaluronidase (bovine testis) for 6 days.

No. of animals treated	trauma	Adhesions of intestines	Adhesions to scar
12	Mechanical	0	1 Thin adhesion
10	Talc	0	4 Dense adhesions

GROUP 4.

Traumatization by Talc, or Talc Controls.

Five animals were used and 100 mg. of talc suspended in 5 cc. physiological saline was injected into the uninjured peritoneum to study the effect. Laparotomy was avoided for the reason that

so much talc was concentrated on the peritoneal surface of the wounds in operated animals.

In clinical cases after operation probably less talc would be concentrated on the inner surface of the wound, because they remain on their backs in bed. Talc is heavy and would probably sink away from the ventral parietal peritoneum towards the intestines, mesentery and cavities.

Rabbits recover 30 minutes after operation and immediately sit on all fours, so that if electric potential attracts talc to the injured area, posture would certainly be an added factor.

We see therefore that as far as posture is concerned experimental and clinical cases adopt the opposite attitudes after operation.

Results. Five rabbits injected with talc fed poorly for 3 to 4 days. Diarrhoea was not seen, as stated by so many other writers, but in these animals 100 mg. was used, and in the literature we usually read of 250 mg. being used.

One animal deteriorated in condition after 7 days and showed signs of obstruction.

All animals were sacrificed after 14 days.

In all cases most of the talc was found to be encapsulated around the liver and lesser omentum. Adhesions encapsulated the talc granules and bound them into small rounded particles the size of small lead shot.

In one case the talc penetrated the peritoneum covering the liver and appeared to be encapsulated in the subperitoneal surface of the liver.

Small talc nodules were seen scattered over the large intestine and none were seen over the small intestine. Delicate adhesions were found binding small intestine to large intestine, and in two cases dense adhesions impossible to separate.

Talc treated cases: Group 3.

In the ten treated animals the talc was much more scattered. Little or no talc was found near the liver. The small intestine showed no talc, as in the controls, but this is probably due to peristaltic movements.

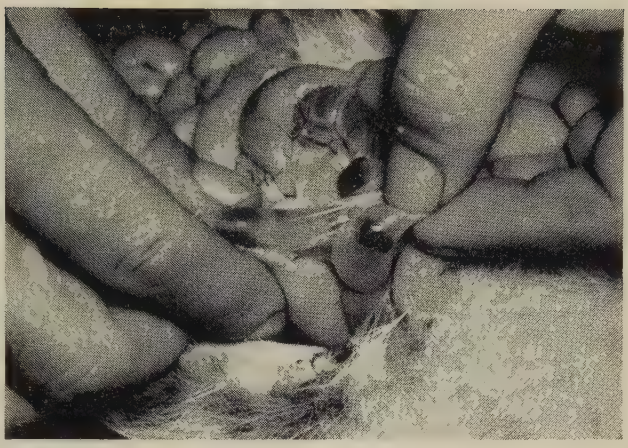
Small scattered nodules, but sometimes large, were found covering not only the large intestine, but also the parietal peri-

Original Work.

Mechanical Trauma.

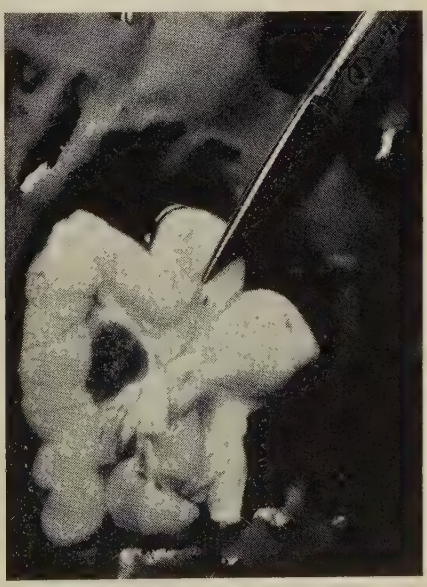
All the photographs seen below were taken at obduction 14 days after trauma.

Treated by Hyaluronidase prepared from a bacterial origin for 3 to 6 days, 12 out of 15 animals formed adhesions in the small intestine as shown in this photograph.



The small intestine of another animal treated as above. This animal formed many adhesions which caused the intestinal stasis demonstrated here.

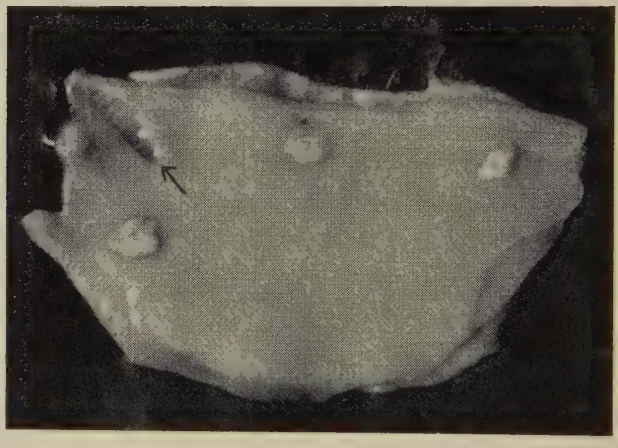
Hyaluronidase prepared from testicular extract prevented adhesions in all 12 animals treated for 6 days. A loop free from adhesions is shown here. The scissors points to a thread suture applied over a perforation at trauma. No adhesions or delayed healing occurred.



Talc Trauma. (100 mg)

Most of the talc is dispersed by treatment with hyaluronidase. Large talc deposits are seen here on the colon. No adhesions formed in this animal.

Fig. 7.



A piece of parietal peritoneum excised 14 days after trauma and treatment. Several dispersed talc deposits are seen but no adhesions. Note clamp trauma at arrow, a serious mistake if practised at surgical operations.

Fig. 8.

Talc plus trauma double the chance of adhesion formation. In spite of treatment adhesions and dispersed talc are both seen here at the abdominal scar.

Fig. 9.

toneum and as mentioned before the inner surface of the wound where most of the talc was found.

Figures 8 and 9 show talc on the parietal peritoneum and the inner surface of the wound. In treated cases no adhesions were seen between intestines, but 4 out of 10 animals formed adhesions to the scar.

In one treated case the beginning of a talc granuloma was seen extending into the wall of the large intestine where it was adherent to the inner suface of the wound. (Fig. 7.)

GROUP 5.

Trauma with 3 % Tincture of Iodine.

Five animals were used to study the effects of application of Tincture of Iodine to a loop. Laparotomy under general anaesthesia was performed, and a loop was delivered. The Iodine was applied with a small gauze swab. In each case 10 to 20 drops was the amount used and the excess was dabbed after trauma. The peritoneum was closed.

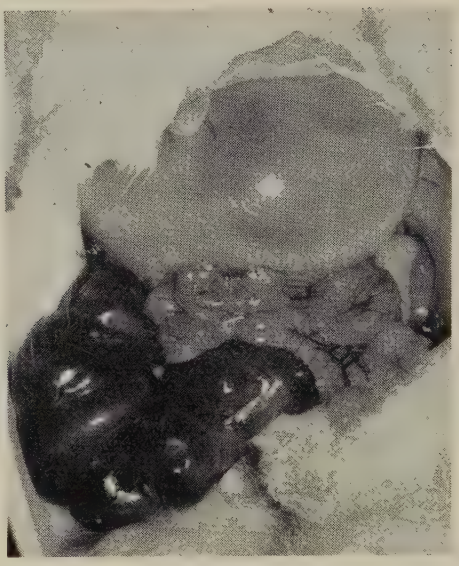
The results were most alarming. Two animals died after 24 hours. Post mortem showed similar results in both. There was no peritoneal fluid. The traumatized bowel was pale, avascular and collapsed. A sticky exudate agglutinated the neighbouring loops to the injured loop, and gross dilatation of the stomach occurred in both animals. (See fig. 10.)

Two animals died after 48 hours. At obduction both showed an acute haemorrhagic peritonitis. Abundant fibrinous adhesions were found. There was excess peritoneal fluid, a paralytic small intestine, distended with gas, and gross dilatation of the stomach. (See figs. 11 & 12.) In one animal the entire inferior surface of the liver was already adherent to the lesser curvature of the stomach.

The remaining rabbit died on the 5th day. Its small intestine was a mass of adherent loops. Proximally there were both ileus and perforation due to the distal obstruction. (See figs. 13 & 14.)

This experiment shows us that Tincture of Iodine causes not only peritonitis but also the formation of massive adhesions.

Trauma to Visceral Peritoneum with 3 % Tincture of Iodine.



After 24 hrs. Exudate adhering loop of gut. Note Acute Dilatation of Stomach.

Fig. 10.

After 48 hrs. Acute haemorrhagic peritonitis with dilated jejunum and many adhesions.

Fig. 11.

The same small intestine seen just distal to the stomach in a state of paralytic ileus. Note abundant adhesions.

Fig. 12.

Trauma to Visceral Peritoneum with 3 % Tincture of Iodine.

After 5 days. Small intestine shows a large mass of adherent loops.

Fig. 13.

The same rabbit. Proximal to the mass the small intestine shows gross dilatation and perforation.

Fig. 14.

GROUP 6.

Treatment of formed adhesions by surgical division and hyaluronidase.

To demonstrate the treatment in formed adhesions, ten rabbits were operated and an attempt was made to produce adhesions. To achieve this a thin catheter was left in the peritoneum and stitched to the skin as in fig. 4.

The difficulty with this method is that only 20 % of animals formed adhesions in this way in previous experiments. To make more certain that adhesions would form, the catheter's peritoneal end was split into four, and 10 mg. talc inserted into this split end. This would double the chance of adhesion formation.

It was thus expected that all animals would easily form adhesions from the abdominal scar to the intestine, and that such adhesions could easily be divided at a second operation.

The ten animals were so treated in a first operation and after 14 days were subjected to the second operation. A paramedian incision was made so as to inspect the first midline incision for adhesions.

Inspection proved that not a single animal formed adhesions at the site of the tube, but all ten wounds were unhealed on the inner surface due to talc. The explanation can be attributed to the fact that the tube was split which allowed a soft movable peritoneal end, and this might eventually prove to be a way to insert a drainage tube with more safety.

Adhesion formation was seen in all animals between the small and large intestine where the talc (N. B. only 10 mg.) had descended in the interval. Slight adhesions were found in other areas.

Adhesions between large and small intestine were separated by sharp and blunt methods. About 8 cms. were separated in each animal. Before the abdomen was closed 2000 units of hyaluronidase were inserted in 5 ccs. saline.

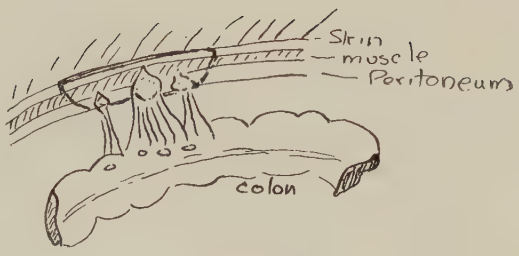
Three animals died of shock within 24 hours.

Intraperitoneal injections were given at 24 hour intervals until 6 treatments were given in the remaining 7 animals.

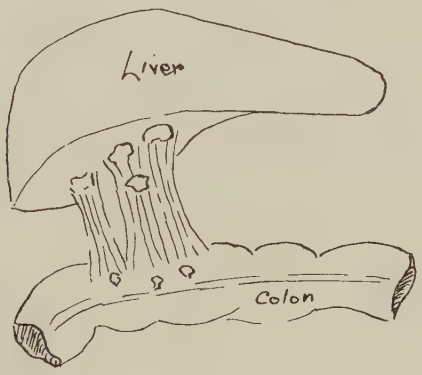
Obduction was performed after 14 days to see the result.

In all 7 animals the separated areas between the intestines were

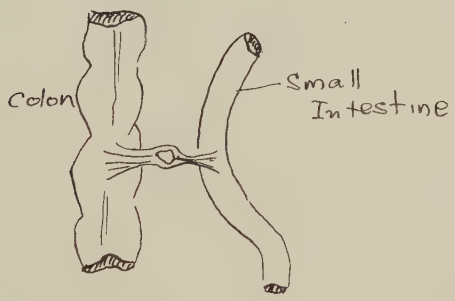
Unhealed wound. Talc in scar and on colon. Dense adhesions.



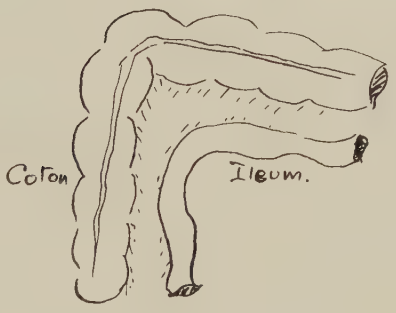
Talc on liver and colon. Dense adhesions.



Talc in centre of adhesions.



With hyaluronidase no adhesions in separated area.



Surgical division of adhesions.

free from adhesions, but adhesions with demonstrable talc as the cause was seen in other areas.

In two animals massive adhesions formed from the unhealed, talc irritated wound to the large intestine. Talc could be seen in the centre of the adhesions.

In five animals adhesions were found in other areas between intestines, with talc nodules in the neighbourhood of the adhesion in every case. In one animal a large talc nodule was encapsulated in the centre of an adhesion.

In another animal a broad inflamed looking adhesion bound the colon to the liver.

This experiment demonstrates that hyaluronidase will prevent the reformation of divided adhesions but cannot cope with talc irritation. Much rather must we think that it spreads the talc and more scattered adhesions are formed, possibly after the treatment has ceased.

Photographs of this experiment were unfortunately a failure, so diagrams were made to demonstrate.

The treacherous type of irritation due to talc is demonstrated in this experiment. When thought to be quiescent it is movable, and when thought to have caused its worst irritation fresh irritation is seen weeks or months, and according to other workers many years later.

In divided adhesions, hyaluronidase was succesfull and prevented reformation in all animals.

GROUP 7.

The Effects of Blood in the Peritoneum.

Five rabbits were used. Laparotomy was again performed under anaesthesia. A mesenteric vein was cut in each animal, and 4 to 5 ccs. blood allowed to flow into the pelvic cavity. The abdomen was closed.

Two animals were sacrificed after 10 days and the remaining three after 14 days.

No adhesions occurred in any of the five animals, and the blood was completely absorbed.

GROUP 8.

The Effect of K 285 (Boots) Starch Powder (for surgical gloves) on the Peritoneum.

Five rabbits were used and 500 mg. of K 285 powder suspended in 5 ccs. physiological saline was injected into the peritoneal cavity of each animal. (In talc trauma 100 mg. was injected.)

The injection probably caused pain, as the animals showed discomfort for 1½ hours. After this period there was no sign of illness and they fed normally.

The abdomens were examined when they were sacrificed after 14 days. Small nodules of the powder still appeared, but little remained. There was almost complete absorption and no adhesions.

This experiment proves that K 285 powder is decidedly indicated as a substitute for talc, and there is no reason why this product should not replace the use of talc completely.

Starch powder for surgical gloves is already used in several hospitals in England, America and Holland.

GROUP 9.

The effect of hyaluronidase on intestinal anastomoses.

To study the effect of the enzyme on intraperitoneal suture lines, and its effect on healing, three rabbits were used. Side to side anastomoses were made in the small intestines.

One animal was kept as a control and the other two received 2000 units of hyaluronidase for 6 days. None of the animals died. Two recovered quickly but one treated animal fed poorly and lost weight.

They were all sacrificed after 10 days. The control animal and one treated animal showed well functioning stomata, and the sections that follow show the difference on microscopic examination.

Healing was not delayed, but the treated animal showed less peritoneal reaction and slightly diminished fibrous tissue around the stitches in comparrison with the control.

The remaining animal showed a patent stoma, but an inflamed loop connecting the stoma. The loop was made too short and caused stasis and peritonitis. It was still red, inflamed, and was distended by hypertrophy and stasis.

A broad dense adhesion was seen connecting the anastomosed area to the greater curvature of the stomach. This was found in spite of treatment. We see here that hyaluronidase does not prevent the formation of adhesions in the presence of sepsis.

Note: The anastomoses were made by Dr. J. Bonnet, chief assistant to Professor Dr W. F. Suermondt.

GROUP 10.

Hyaluronidase in the septic peritoneum.

Six animals were used in this experiment to determine the effect of hyaluronidase when sepsis is present in the peritoneal cavity.

In all the animals laparotomy was performed under anaesthesia, and a purse-string applied 1 cm. from the tip of the appendix. The purse-string was then pulled and firmly tied. The distal portion was opened, the appendix returned into the abdomen, and the wound closed. This was intended to induce sepsis.

Two animals were left untreated as controls. Two were given 2000 units hyaluronidase daily for 6 days, and two were given 2000 units hyaluronidase plus 50.000 units penicillin daily for 6 days into the peritoneal cavity.

None of the animals died, and they were sacrificed after 2 weeks.

The two controls recovered and fed normally. They showed no signs of fever and weight remained steady at 1½ kgm. At post mortem they showed massive adhesions and walled-off pus in the pelvic cavity. There was no spread of infection.

The two that received hyaluronidase only, showed signs of generalized illness, fever for 6 days, and each lost 500 gms. in weight. On post mortem examination no pus, and less adhesions were found, but the parietal peritoneum was still red, inflamed, and thickened. Low grade peritonitis persisted.

The two animals that were given hyaluronidase and penicillin fed poorly, both showed fever for 5 days and each animal lost only 250 gm. in weight. At post-mortem adhesions were seen but less massive, and no pus or peritonitis could be detected.

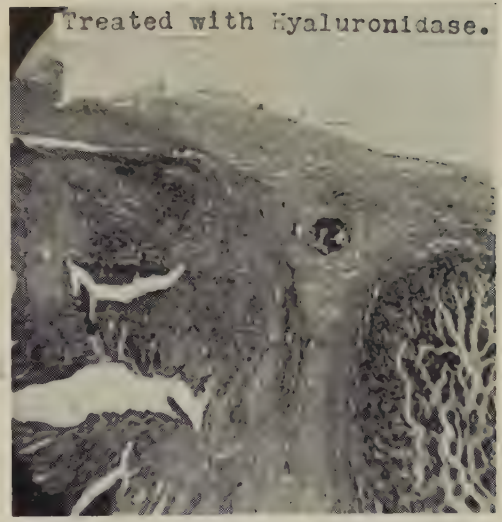
This experiment was most useful in demonstrating:

a. That hyaluronidase should not be used in the septic peritoneum.

Studies of anastomoses.

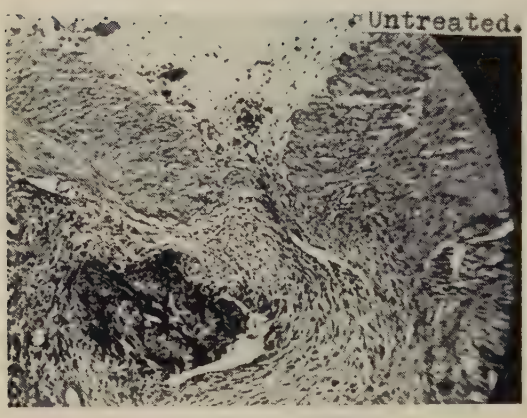
Sections after 10 days

Here is seen the stoma, stitches, and gross peritoneal reaction.

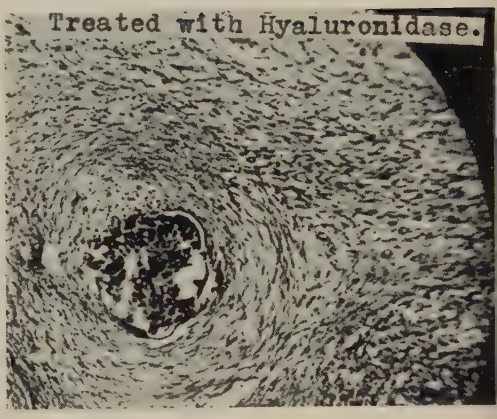


Here, less peritoneal reaction.

Sections after 10 days



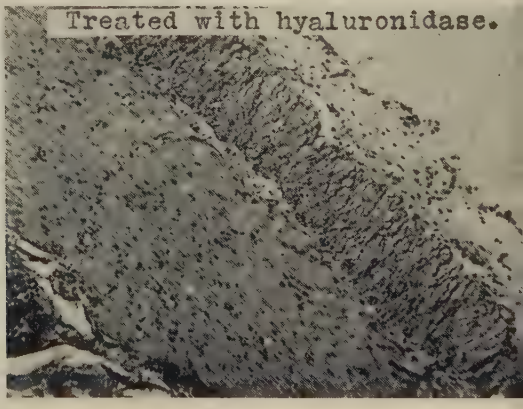
Gross fibroblastic reaction is seen surrounding a stich in this section.



In the treated case the reaction is only very slightly diminished.

Sections after 10 days

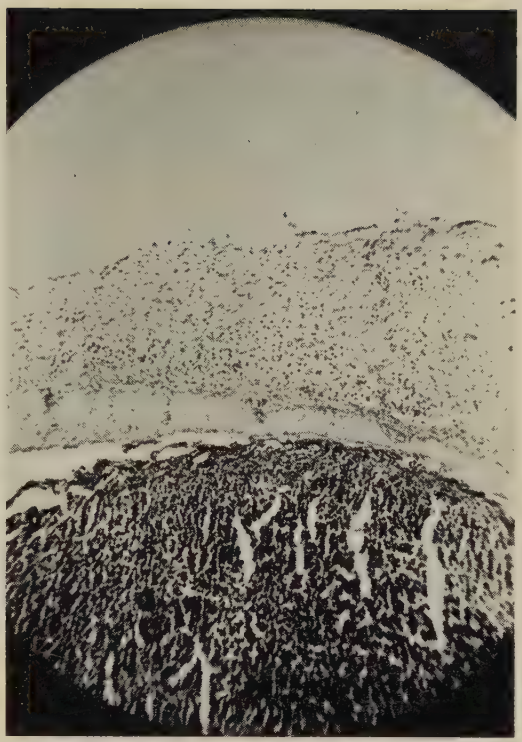
Here we see mucosa, muscularis, and gross inflammatory reaction of serosa.



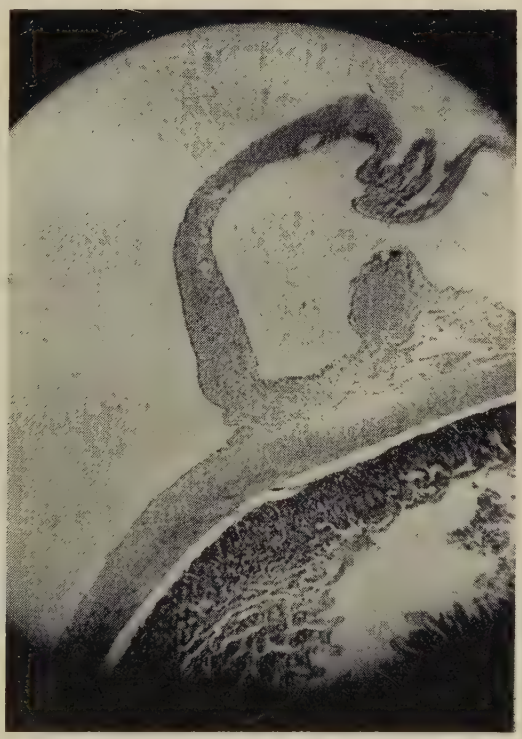
The same layers are seen here, but the serosa shows less reaction.

Original Work.

Hyaluronidase is contra-indicated in the septic peritoneum. In the presence of infection its protective action is prevented. Sepsis is a common cause of adhesions, even in the abdomen which has not been opened.



An infected peritoneum 12 days after operation. The serosa shows gross thickening, many leucocytes, and fibroblasts.



After 12 days. The same animal. In spite of treatment a thick, dense adhesion has formed.

b. That it is safer when given with antibiotics, but still not advisable.

c. That it is useless in preventing adhesions when the peritoneal cavity is septic.

GROUP 11.

Dry swabs and hot lamps on the serosa.

Only two rabbits were used in this group. A loop of small intestine was delivered at laparotomy and rubbed well with dry gauze so as to injure the serosa, but not the underlying tissue.

Immediately afterwards a warm lamp was held directly over the loop to heat and dry it. This was done for five minutes.

At post-mortem after 14 days both animals were completely free from adhesions.

This experiment confirms the fact that the denuded serosa often heals without forming adhesions provided the underlying tissue remains uninjured.

GROUP 12.

Pathological Studies.

The studies were rather histological than pathological, and served to demonstrate sections at intervals in the course of treatment.

The traumatized serosae of treated and untreated animals were also studied to see whether an unwanted effect on healing resulted after treatment with hyaluronidase.

Seven animals were used initially, but several more were sacrificed later to fill in wanted sections.

A detailed pathological study of the difference in treated and untreated sections would be one of tremendous magnitude, and this was not attempted.

The microphotographs that follow are self explanatory.

In the rabbit we see leucocytosis in the section 4 hours after trauma. In general we can say that sections in treated animals show a mild depression of leucocytes, fibrin and fibroblasts. In treated animals the peritoneal reactions are obviously less marked.

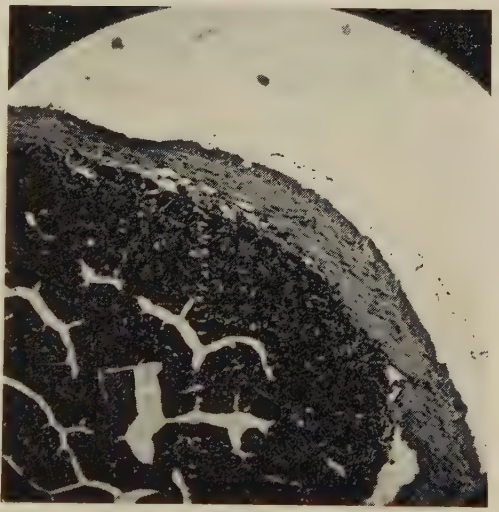
There is no sign of delay in healing of muscle in sections of

anastomoses, and the serosa is healed. As in other sections, the serosa shows less reaction than that of the untreated animal.

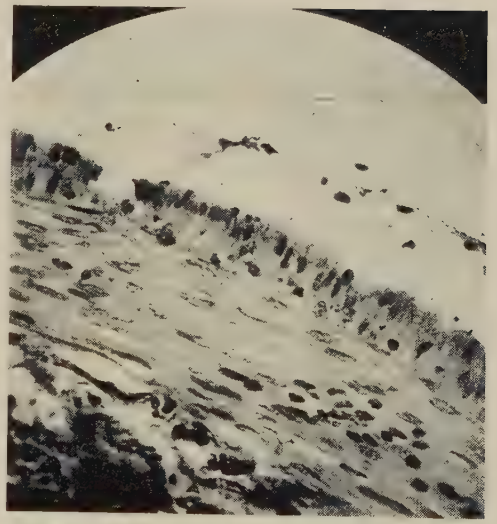
The sections show that healing of the serosa occurs with great rapidity in treated animals.

Note: The microscopic investigations, sections and photographs were made in the Laboratories for Pathological Anatomy in the Department of Professor Dr G. O. E. Lignac.

Histological studies of treated and untreated sections.



Normal serosa.

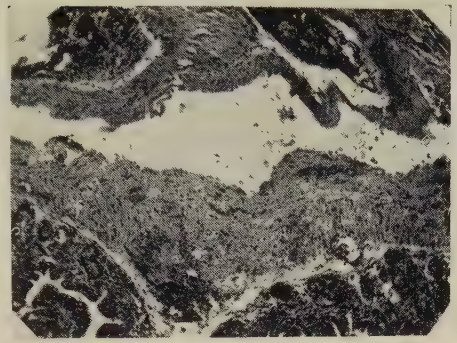


Normal serosa. High power.

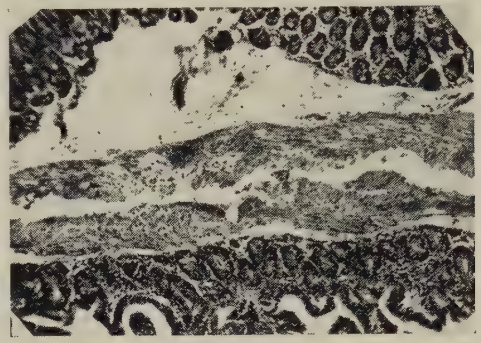
MECHANICAL TRAUMA.

After 30 minutes.

Untreated.



Treated with Hyaluronidase.

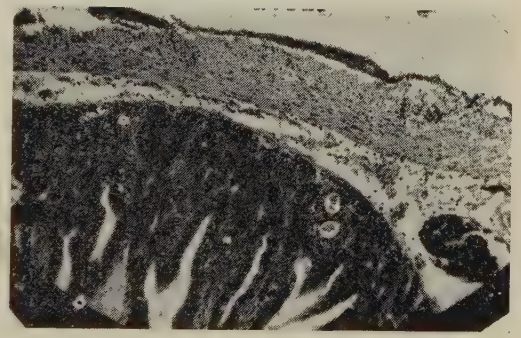


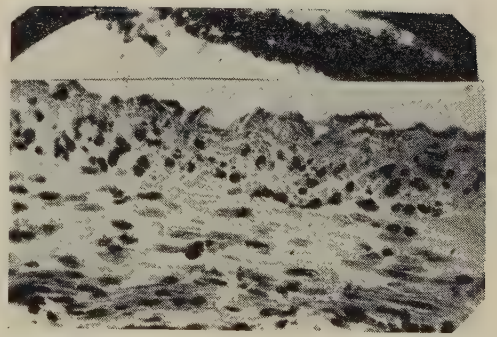
In these sections we see mucosa, muscular layers and no serosa. Injured surfaces are approximating, and the capillaries show hyperaemia. They show no difference.

After 4 hours.

Untreated.

Untreated.

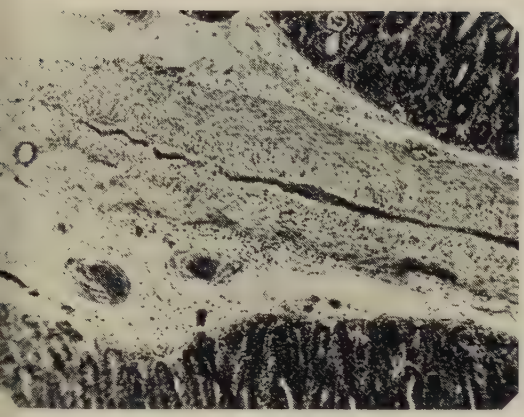




Low and high power studies of exudate and leucocytosis. In rabbits leucocytosis is noted after 4 hours.

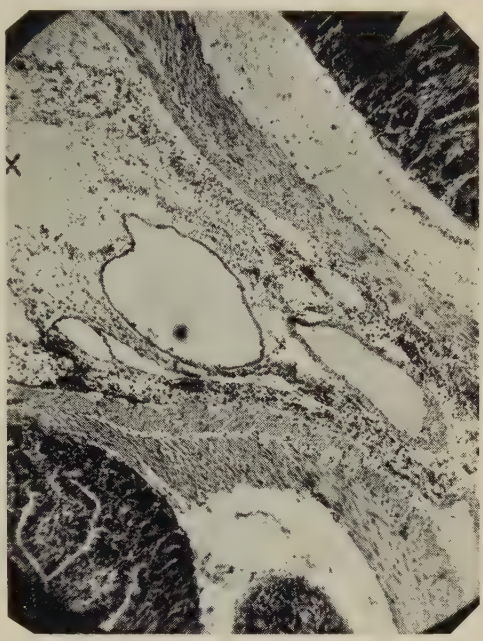
After 4 hours.

Untreated.



Two traumatized areas show approximation. The sticky exudate holds them together. Note the leucocytosis. After 4 hours.

Treated with hyaluronidase.



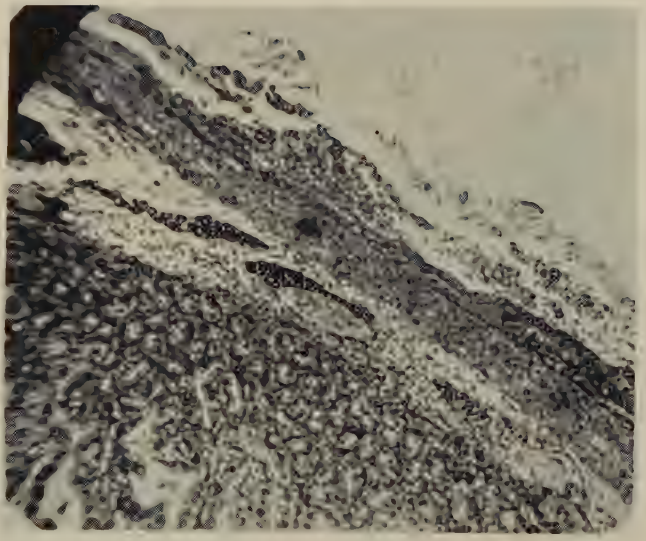
Only a small portion of the traumatized area is seen here above and below X. There is no approximation of the injured surfaces. Leucocytosis is seen. Most of the centre, between the muscular layers, is adjoining mesentery.

Untreated.

High power study. The arrows point to the early stage of an adhesion.

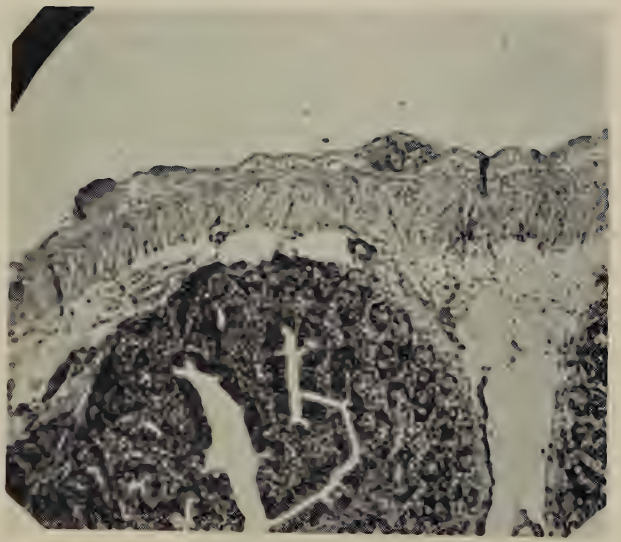
After 24 hours.

Untreated.



Serosa shows reactionary peritonitis, exudate, fibrin, and leucocytosis.

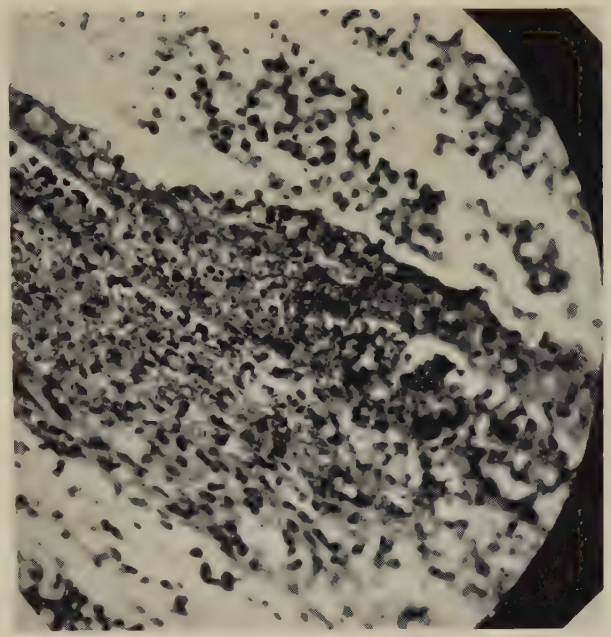
Treated



Here much less exudate is seen, less fibrin, and fewer leucocytes in exudate, muscle and submucosa.

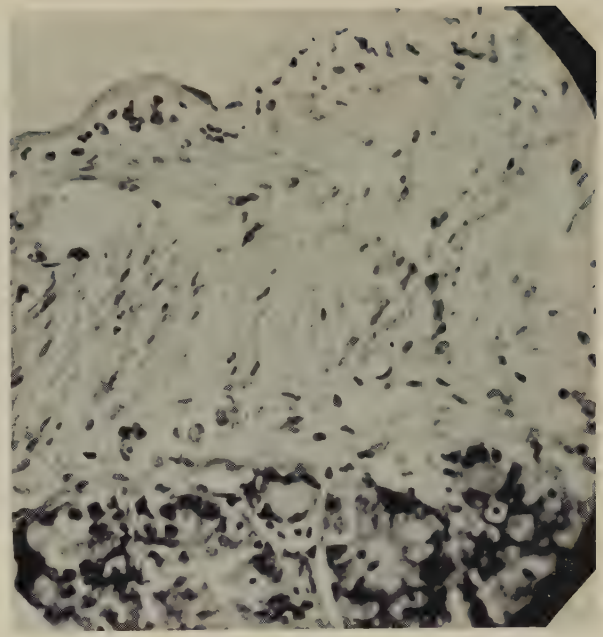
After 24 hours.

Untreated.



On high power the fibrin is seen more clearly. There is no sign of the serosa healing.

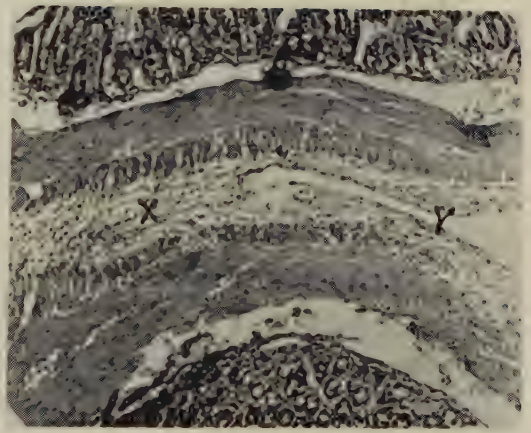
Treated.



In the treated animal there is no peritonitis. The serosa is healing. A possible histiocyte is seen on the serosa. There is less fibrin visible.

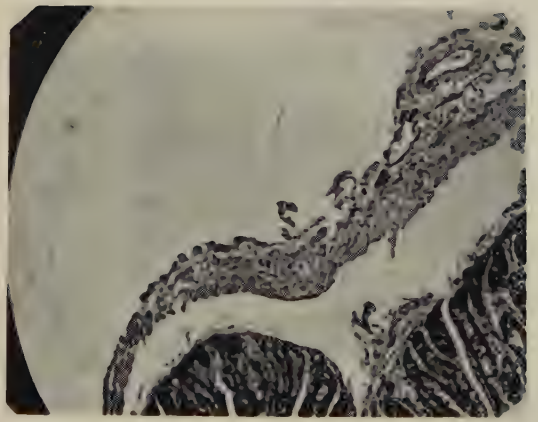
After 6 days.

Untreated.



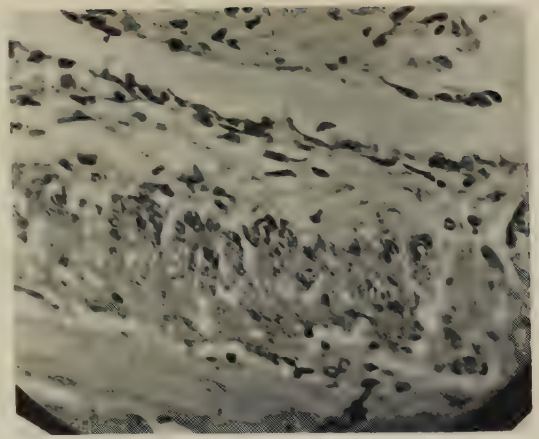
A strong adhesion is seen at X, with fibroblastic invasion.

Treated.

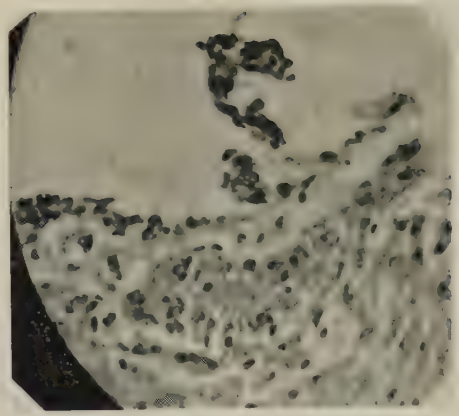


Although serosal surface is still irregular in some areas, no adhesion has formed.

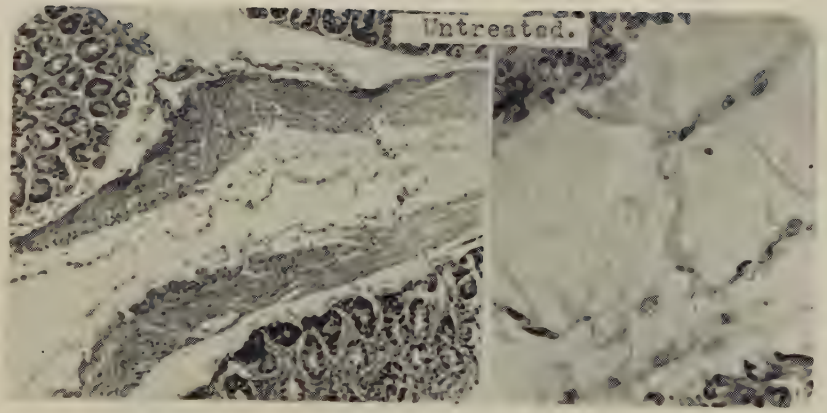
After 6 days.



Fibroblasts seen under high power. This microphoto was taken of the section above at Y.

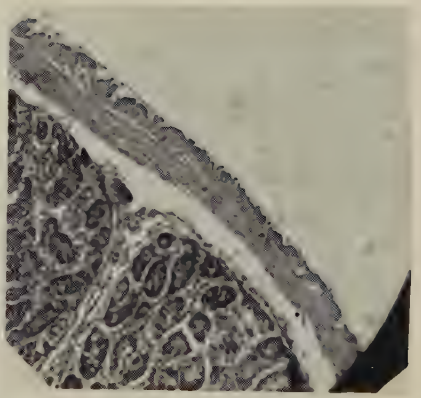


Magnified view of the section above.



A thin adhesion, well developed after 12 days. Fibroblasts are seen.

Magnification of same adhesion.

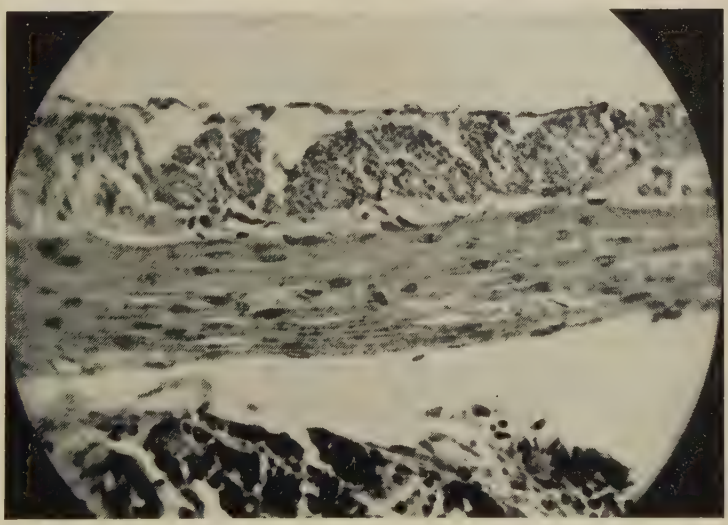


12 days. A treated animal. The serosa has healed.

An untreated animal. A dense adhesion after **12 days.** Firm connective tissue has replaced the fibrin.

A fully developed adhesion. Fibroblasts and fibrocystes seen under high power. The section was taken from an untreated animal after **14 days.**

After 12 days.



A treated animal showing the serosa completely healed. There is very little fibroblastic tissue visible.

CLINICAL WORK.

Case 1.

Mrs de W. L.

Age. 40. Occupation. Stage and social work.
Admitted 23rd. July, 1952.
Complained of pain in the lower abdomen.

Present Illness.

The pain was of a crampy nature and became unbearable on occasions. It was never completely relieved after the operation for adhesions in 1951, and her present pain was the same as before that operation.

Previous Illnesses.

In 1932: Appendicitis. The appendix was removed through a paramedian incision.

In 1951: Operation for Adhesions, through a lower abdominal midline incision.

At this operation multiple adhesions were found. The appendix stump was completely adherent to the sigmoid colon. Dense adhesions of omentum, small and large intestine had formed a matted condition in the pelvis. The sigmoid colon was pulled to the right and the caecum drawn well to the left by fibrous adhesions. There was no ovarian or tubal cause for the adhesions.

Physical Examination.

General. The patient was 15 pounds under weight.
Temp. Normal. Pulse. Normal. Urine. Normal.
Cardio-Vascular System. Heart good, B. P. 120/80.
Blood. Normal. Haemoglobin. 85 %.
Abdomen. Tender on palpation below umbilicus and bulky in Iliac fossae.
Bowels. Normal. At rectal and vaginal examinations thickening could be felt of the pelvic contents.
Vaginal speculum. Mild endocervitis.

Diagnosis. Chronic parametritis or reformed adhesions.

Operation. 24th July, 1952. (Performed by the writer.)

A right paramedian incision was made and the pelvis inspected. Reformed adhesions in fair sized bands were found, but were less

than those found in 1951. The adhesions were carefully divided and ligated with plain catgut. On the recommendation of a gynaecologist total hysterectomy was also performed.

No inflammation of tubes or ovaries was seen.

(Surgeons washed their gloves before both operations).

Hyaluronidase 4000 units in 20 ccs. Physiological saline was injected for 6 days. Injections were given through the thinnest catheter stitched in situ. They were given at body temperature.

After 6 months the patient was examined and showed no clinical evidence of reformed adhesions. As she was thin most of the pelvic contents could be palpated bimanually, and no bands or thickening could be felt.

CASE 2.

Mrs. M. J.

Age. 38. Occupation. Housewife.
Admitted Feb., 1953.
Complained of acute epigastric pain.

Present Illness.

Pain since 1945, of a colicky nature in the epigastrium. Attacks came on at intervals varying from weeks to several months. For two months the pain became steadily worse and more frequent, and often caused vomiting. She desired to have an operation for relief of the condition.

Previous Illnesses.

1925 Appendicectomy.

1937 Gall bladder operation. (Type unknown). Records could not be traced.

1942 Operation for adhesion in upper abdomen at Groote Schuur Hospital.

1945 Rt. kidney removed for pyo-nephrosis.

1952 Severe pyelo-nephritis. Cured by medical treatment.

Physical examination.

General. Still well covered, but lost 20 pounds in 6 weeks. There was mild icterus of the conjunctivae.
Temp. Normal. Pulse. 75. Urine. Normal.
Blood. White count normal. Haemoglobin. 87 %.
Cardio-vascular System. B. P. 118/80.
Pulmonary & Nervous Systems. Normal.
Bowels. Constipated.
Abdomen. Tender epigastrium.

Diagnosis. Adhesions.

Pre-operatively Vit. K. and Calcium were injected.

Operation.

A left upper paramedian incision was made. A mass af adhesions were found binding into one mass the liver, stomach, duodenum, transverse colon, greater and lesser omentum, and the gall bladder. After all the adhesions were divided and ligated, a small atrophic gall bladder was found. It was removed and the common duct was drained.

Hyaluronidase 4000 units in 20 ccs. normal saline was injected intraperitoneally for 6 days as in Case 1.

Five months after operation she was still quite well.

Case 3.

Mrs. E. D.

Age. 27. Occupation. Housewife.
Admitted. 29th July, 1952.
Complained of pain in the lower abdomen on the right.

Present Illness.

Pain was persistent for 14 days and kept her awake. There was no vomiting during this time.

Previous Illnesses.

Patient had two children and one miscarriage, but she had undergone no operations.

Physical examination.

General. There was no obvious loss in weight, but she looked reasonably ill.

Temp. 100.5° F. Pulse. 102/min.

Cardio-vascular System. B. P. and Heart normal.

Lungs. Normal.

Bowels. Constipated. Urine. Acid and mild albumin but no pus cells.

Blood. White Count 30.000. Haemoglobin. 90 %.

Abdomen. Tender in Right Iliac Fossa and fullness felt.

Vaginal and Rectal Examination. A lump was felt attached to the uterus on the right side.

Diagnosis. Pyosalpinx.

Treatment.

General. Procaine penicillin 400.000 units daily.

Operation.

Operation was undertaken on account of persistent pain and temperature of 99.2° F. after three days observation.

A small pyosalpinx was found which could be removed intact. There was no sepsis outside the tube.

Extensive pelvic adhesions, which were of the chronic fibrous type, were found and required division. A tube was stitched in situ, and as the temperature subsided completely after 24 hours, 6 hyaluronidase treatments were given as in the previous cases.

Penicillin was continued to prevent possible spread of infection.

This woman made an uneventful recovery and was discharged on the 12th day. Six months after operation she was still quite well.

Case 4.

Mrs. M. S. K.

Age. 61. Occupation. Housewife.
Admitted. 9th June, 1952.
Complained of pain in the Right Hypochondrium.

Present Illness.

Pain for 6 months, but unbearable pain for 10 days, requiring daily injections of pethidine for relief of pain.

Previous Illnesses.

Varicose veins for 15 years, and varicose ulcer for 3 years.
Trendelenburg operation in 1951 which failed to cure the ulcer.
The patient had undergone no previous operations.

Family History.

One brother has sugar in the urine, and lumbar sympathectomy was performed for failing circulation in one leg.

Physical examination.

General. Obese patient. Looked tired after days of pain and loss of sleep. There was no jaundice.

Temp. 99.5° F. Pulse. 80. Urine. Normal.

Cardio-vascular System. Heart good. B. P. 180/100.

Sphygmo-oscillometer showed very little response at the ankles, which threw some light on the unexplained persisting ulcer of the leg.

Blood. White count within normal limits.

Lungs and nervous system: normal. Bowels. Normal.

Abdomen. Gall bladder tender to palpation, and a lump was felt

in the pelvis which was a uterine tumour of considerable size on vaginal examination.

X Ray examination confirmed multiple gall stones.

Operation.

The gall bladder was removed through a Mayo-Robson incision. Massive adhesions were seen which were divided and ligated. The uterus was felt and thought to be carcinomatous, and it was decided to remove this at a second operation.

Hyaluronidase treatment was given at the first operation. When the second operation was performed no adhesions could be felt in the upper abdomen.

(The second operation was done 14 days after the 1st).

Two Typical cases that require hyaluronidase treatment.

Case A

Mrs. M. M.

Age. 48. Occupation. Housewife, and social worker.

Complaint: Seen at home for two years for attacks of colic, which come on once a month but recently as often as two attacks a week.

Present Illness.

Pain in epigastrium since 1938. Onset of pain is slow and increases in intensity until a few hours have been endured. Injection of morphia gr. ½ is then required to relieve it. The onset of pain is related to costive bowels, so if she neglects such care an attack is sure to follow.

Previous Illnesses.

Operations:

1928 Appendix and Rt. ovary removed. A drainage tube was inserted.

1934 Operation for retroversion and ovarian cyst.

1941 Uterine fibroid removed.

1944 Upper abdominal operation for adhesions.

1949 Another operation for adhesions.

For some reason the omentum was also removed at this operation.

Physical examination.

General. Weight 110 pounds. Actual weight lost. 30 pounds.

Temp., Pulse, Urine, and Blood: Normal. B. P. 110/80.

Bowels. Constipated with an attack, and then a sudden serious diarrhoea follows with 15 motions a day, sometimes for two days.

During an attack one can palpate and percuss an obvious lump in the light hypochondrium which feels like obstructed intestine. Visible Peristalsis is also seen.

The patient refuses operation because two previous operations for adhesions failed.

Hyaluronidase treatment is indicated in this case.

Case B.

Mrs. G. V.

Age. 38. Occupation. Housewife.
Admitted. May, 1952.
Complained of severe pain on the stomach and vomiting.

Present Illness.

For several weeks there has been crampy pains in the abdomen, but severe pain for 48 hours.

The cramps were mild when they first appeared and subsided after a few minutes. Every 15 to 20 minutes the pain returned and seemed to be worse every time. For 48 hours the attacks were more frequent and she vomitted every time before the pain subsided.

She was unable to retain any form of nourishment during this period.

Enemas, medicine and injections did not help.

The patient insisted that this illness was identical to the severe illness she experienced in 1951 when she had obstruction of the bowel.

Previous Illnesses.

Two children.

In 1950 Operation for appendicitis and sterilisation.
In Feb. 1951 Operation, obstruction due to adhesions.

Physical Examination.

Patient looked exhausted and dehydrated, but her pulse and temperature were normal. The heart was good, and B. P. 120/80.

Blood. Within normal limits. Urine. Scanty, but normal.

The Abdomen was tender only during attacks and although the patient was thin visible peristalsis could not be seen.

Straight X ray showed no gas in the small intestine.

The surgeon injected 4 ccs. prostigmine which caused visible

peristalsis and a lump became visible on the left side of the umbilicus.

Operation was performed immediately and inspection of the bowel confirmed the diagnosis of obstruction. Two feet of small intestine were freed from reformed adhesions, worse than those divided in 1951.

Prognosis. The surgeon thought reformation was to be expected.

Hyaluronidase treatment is strongly indicated in such a case.

A Case treated at the University of Leiden Hospital.

Mr. Theunis G.

Age. 65. Occupation. Retired. Worked all life in fishing industry.
Admitted. 4th August, 1953.
Complained of abdominal pain.

Present Illness.

Two months after his operation in 1951, his complaint returned. There is pain with meals and at night, relieved by a glass of milk. The pain has recently increased in severity, and if he does not rest sufficiently, the pain radiates towards the precordium.

He has never suffered from heartburn, but on occasions eructation of gas occurs.

Since the last operation there has been no haematemesis or malaena, but he is always inclined to be constipated.

Previous Illnesses.

1932 Perforation. Stomach operation. ? Oversewing.
1949 Haematemesis. Reoperated.
1951 Malaena. Reoperated for stomach.

Family History.

One brother had a stomach operation.

Physical Examination.

Pulse and temperature normal.
Heart enlarged on left. B. P. 190/90.
Circulation. Arterial pulsation normal.
Urine. Reaction neutral, albumin trace.
C.N.S. Normal.
Blood. White count normal. H.B. 77 %.
Rectal Examination. Nil. Nocturia 1 to 3 times.

Operation. By Dr. Bonnett, Chief assist. to Prof. Dr. Suermondt. Excision of old midline incision. A residual ulcer was found

after a Billroth I resection, and a Billroth II was performed at a second resection.

Massive adhesions were found from stomach to liver and anterior abdominal wall, which were divided with great difficulty. A large infiltrated area was found. Dissection was completed to free pancreas, bile ducts and duodenum. Another $^1/_3$ of the remaining stomach was resected, and a retrocolic gastro-enterostomy completed.

Hyalurodinase, 8000 units Benger in 250 ccs. of physiological saline, was instilled at the end of the operation. This was repeated daily for 5 more days by paracentesis. On the third and 4th days 150 ccs. were used as solvent as the patient had flatus and bowels had not yet acted.

A vacolitre was used from which the solution was run into the peritoneal cavity. Discussion of the case follows later.

CHAPTER X.

DISCUSSION.

The study of adhesions has been steadily advanced through the last century.

In all branches of surgery and medicine rapid progress has been made in technique and therapy.

Modern methods and drugs, combined with knowledge and experience have brought us to a satisfactory approach to the treatment and prevention of adhesions.

In 1911 Richardson recognised the short time in which adhesions are formed.

Hertzler (1921) did further study and demonstrated the continuation of the process of adhesion formation.

In 1944 the complete process was studied by Steinberg.

The classification of the causes, according to Boys (1942), is most satisfactory. He mentions four main causes.

A. Traumatic.

B. Bacterial.

C. Thermal.

D. Chemical.

To this it would be wise to add:

E. Foreign body causes, and

F. The physiological cause or the inherent tendency.

A. *Traumatic.* Rough handling of the peritoneum has been blamed by several authors as a cause. From the literature we can see that injured serosa alone is enough to be a cause.

Although Robbins et al. (1949) found denuded serosa insufficient trauma to produce adhesions, Thomas & Rhoads (1950) found that 31.9 % of animals formed adhesions from denuded serosa.

Rhodes (1949) found that denuded areas regenerate, but form adhesions when oversewn.

There is variation in results. We can explain by saying that it is extremely difficult to remove serosa without injuring the underlying tissue.

In original work only two rabbits were used as a test in Group II. The serosa of an intestinal loop was rubbed with a dry gauze swab, carefully enough to preserve underlying tissue. Both animals failed to form adhesions.

Thomas & Rhoads used 40 animals, and mention their care in protecting underlying tissue. We must accept their observation that adhesions result from denuded serosa.

If tissue underlying the serosa is injured as well, as in applying an artery forceps to the peritoneum, (see fig. 8) or in severe scraping of serosa and underlying tissue, a high percentage of rabbits form adhesions. In original work, 31 traumatized animals were used in studies and control experiments, in which underlying tissue was also injured. Of these rabbits at least 90 % formed adhesions.

In surgery therefore, we should accept that injury to the serosa is always dangerous. It is impossible to know when serosa alone, or serosa and underlying tissue are injured, and gentleness to the peritoneum should be part of the surgeons responsibility.

Other common instances of trauma may be found in the use of dry packing swabs, and heavy retractors. Sponging too hard with dry swabs could cause injury even to the underlying tissue. We often see a subserosal haematoma due to pressure alone.

The exploratory wound in every operation is the most regular peritoneal injury. Adhesions to the interior surface of an old wound is common, and the omentum is most frequently adherent because of its obedience to electric potential. In original experimental animals 16 % of controls formed adhesions to the wound.

Clinically two precautions are important in protecting the peritoneum when closing the wound.

A. Clamps and artery forceps should be applied to the peritoneum with great care. They should be applied to a narrow portion of peritoneum. If two or three centimetre widths of peritoneum are clamped, the whole injured area cannot be everted with closure of the peritoneum. We must remember that a clamp

or artery forceps causes injury to underlying tissue as well; a sure method of producing adhesions.

B. It is essential to use an everting peritoneal stitch of the continuous type.

This method has been favoured in America for many years, but is not employed by all surgeons. Methods of stitching are compared in the illustrations that follow.

Blood in the peritoneal cavity must be considered with mechanical trauma.

According to Hertzler (1935) auto-blood is absorbed within ten hours. He states that coagulated blood begins to absorb when serum is separated from the clot. The solid material takes weeks or months to absorb either by means of phagocytosis, or may liquefy from exudation and then be absorbed. Hertzler advised that one should prevent contact of blood with denuded surfaces of serosa.

In original experiments 5 animals were used and 5 ccs. of blood allowed to bleed from a mesenteric vein into the peritoneal cavity. They were sacrificed after 14 days.

Adhesions did not form in any of these animals, and no trace of blood could be found.

It is quite clear that blood does not traumatize the peritoneum. If adhesions occur from blood clot in contact with a traumatized area we must blame the traumatized area for the formation of adhesions. If blood clot is added to a denuded area, it could serve as substantial scaffolding for the fibroblast to enter, and this would facilitate the formation of adhesions.

There is up to the present no evidence that blood in the peritoneum will produce adhesions in the absence of injury to the serosa.

B. *Bacterial Causes.*

Infection is surely the most common cause of adhesions, and this fact is appreciated by all surgeons.

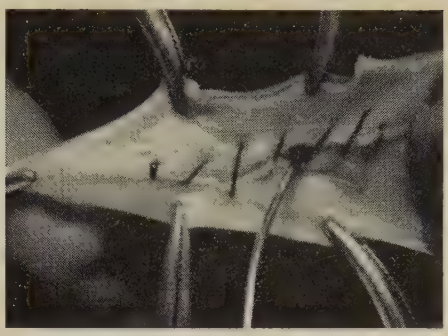
Infection may originate from:

a. Inflammation already present in the peritoneal cavity, as in peritonitis, cholecystitis, salpingitis, etc.

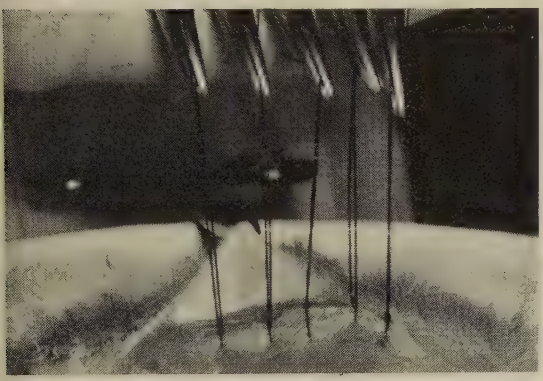
How to close the peritoneum to avoid adhesions.

Photographs of exterior. Photographs of interior.

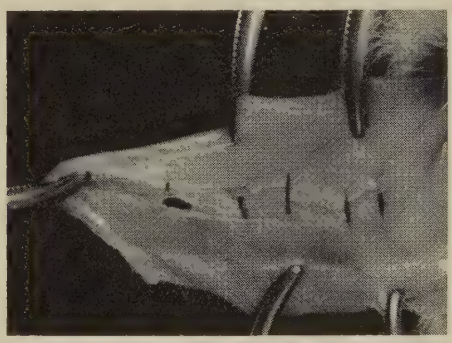
(a). Continuous stitch.



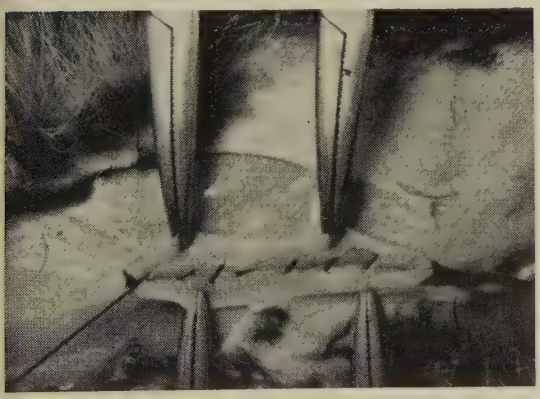
On traction, open and raw areas appear. See pin in orifice.



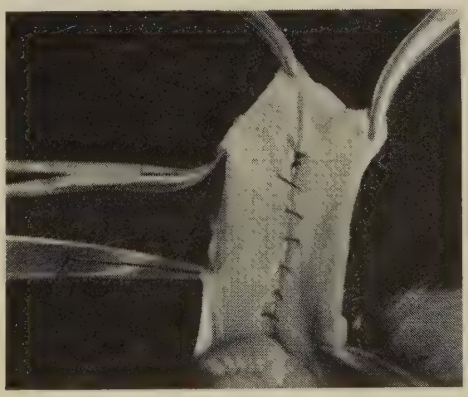
(b). Interrupted stitch.



On traction, open and raw areas appear.



(c). Everting continuous stitch. The best method.



On traction smooth interior surface. (Omentum cannot become attached).

b. Spread from the lumen of an intestine which has become inflamed or obstructed.

c. Insertion of bacteria at operation.

d. The insertion of drainage material into the peritoneum.

In original experiments 6 animals were operated, and the tip of the appendix opened in each animal. All animals formed extensive adhesions due to the septic material liberated.

In one animal which was subjected to intestinal anastomosis, the intestinal loop was too short. The intestine became inflamed, and massive adhesions formed in spite of treatment to prevent adhesions.

Muller and Rademaker (1933) investigated 42 clinical cases who were operated for symptoms of adhesions. Records of previous operations were investigated. They proved that 35 cases had drainage, and 6 others had infection of the wound. In two cases staphylococci were actually cultured from sections of the adhesions. They held that infection was the most important cause of adhesions, and that drainage is always accompanied by infection.

Thermal Causes.

These may by found in the indiscriminate use of the cautery, the application of over hot gauze sponges and inserting intraperitoneal fluid at unnecessary high temperatures.

Using over hot solutions and wet swabs soaked in them is still a common error. Few surgeons have had the pleasure of seeing a sister use a sterile water thermometer to check solution temperatures. It is important to prefer wet swabs to dry swabs in the prevention of adhesions. To make the effort complete it is insufficient for the sister to feel the temperature of solutions. She must use a thermometer and read it.

In emergency surgery, particularly after severe haemorrhage, intraperitoneal saline is sometimes instilled at the end of the operation. Absorption from the peritoneum is so rapid that this method cannot be discarded, but again we look to the nursing staff to make sure of the correct temperature.

When using the cautery, it is for the surgeon to remember that

cauterization will go deeper than the serosa. Underlying tissue will certainly be injured whenever the cautery touches a peritoneal surface. Indiscriminate use can therefore be a cause of adhesions.

Chemical Causes.

Chemicals are usually used in the peritoneal cavity for the prevention or treatment of infection.

To produce a cauterization effect, they are applied to stumps, e. g. of the appendix, fallopian tube, duodenum or cystic duct. They are further used on cut intestinal ends when doing anastomoses or resections.

The most common ones used are pure carbolic, or phenol, silver nitrate, and tinctures of Iodine, Metaphen, or Merthiolate.

For disinfecting purposes solutions of Dettol or Biniodide of Mercury are often seen in the operating theatre for cleansing solutions.

All these chemicals are irritating to the peritoneum, and will cause a local or even a generalized peritonitis unless they are used with great care.

Experimentally, tincture of iodine was applied to the serosa of a loop of small intestine. This was done in 5 rabbits under general anaesthesia. All the rabbits died within 5 days from peritonitis or from obstruction due to massive adhesions.

Tincture of Iodine is comparatively mild if compared with some of the other chemicals mentioned, and it is reasonable to suggest that the above mentioned chemicals should not be used in the peritoneal cavity. There is no reason why they should not be replaced by a strong solution of terramycin, or aureomycin, or a combination of both.

If we take into account the destructive effect of the chemical, with devitalization of the serosa, we can imagine that superimposed infection would be more likely than with the use of an antibiotic solution. Whereas strong chemicals are applied once, there should be no objection to dabbing with antibiotic solution more than once. This should be an advantage in cases where stumps are bulky or moist.

Sulfanilamides irritate the peritoneum if used in powder form. From the work of Crutcher et al. (1943) we see that all sulpha-

nilamides can produce adhesions if applied in fine powder form. The essential method is to apply them in solution. The solutions are absorbed and produce no adhesions.

E. *Foreign Body Causes.*

Foreign substances in the peritoneum cause irritation and infection usually follows.

Gauze swabs that are accidentally left in the peritoneal cavity may cause death due to infection, adhesions and obstruction, or perforation. They have been known to cause intraperitoneal abscess, and have been extracted from a sloughing rectum.

Drainage is an essential procedure in the infected peritoneum, but often drains are left in too long. If this is allowed, foreign body reaction occurs, or the process of encapsulation by fibrous tissue, which results in fibrous adhesions.

In experimental animals, adhesions were found in 3 out of 15 animals when a hard catheter was inserted i. e. 20 % formed adhesions, and that in an uninfected peritoneal cavity.

If the peritoneal end of the catheter is split into four, which makes this end movable and softer, better results are obtained. In original experiments none of the 10 animals treated in this way formed adhesions to the drain after 14 days.

In drainage, therefore, it seems important to:

1. Make the drain as thin as possible.
2. Make it as soft as possible.
3. Split the part which lies in the peritoneal cavity, so that it is softer, causes minimum pressure, and is movable with intestinal peristalsis.

Muller and Rademaker (1933) maintained that drainage caused infection and adhesions in over 40 surgical cases. It seems essential therefore, to administer antibiotics while draining, to counteract infection.

The longer a drain is left in the peritoneum, the greater is the chance of infection.

Drainage tubes should be led into a bottle containing an antiseptic to prevent ascending infection. The tube should be inspected at 24 hour intervals, and removal on each occasion should be considered.

Stitching Material.

Green (1946) considered that excessive stitching material causes adhesions.

This was confirmed by Thomas and Rhoads (1950). Singleton et al. (1952) found more adhesion formation with oversewing denuded areas than without oversewing.

Green thought that peritoneal sutures cause a suture peritonitis, and that no purse string should be inserted to bury the appendix stump. He also stated that unnecessary thick material, and long cut ends should be avoided.

His view on the treatment of an appendix stump is not accepted by the majority of surgeons. The most popular technique is to bury the stump. An unburied stump contains potential infection, and the raw area must produce an exudate. Both factors cause adhesions.

Talc Powder.

Talc powder implantation into the peritoneum may be considered as a chemical or foreign body cause of adhesions.

In spite of extensive work done in the study of talc effects, a large percentage of modern surgeons still fail to realise the crippling results that may follow if this irritant is applied to the peritoneum. After detailed study of its unceasing irritation one can conclude that an accidental swab left in the peritoneum is no greater crime than the application of talc.

The figures below were obtained from weighing 5 smooth Latex gloves at the Leiden University Hospital. The chief chemist made the readings on a very accurate scale. (Mettler, Switzerland.)

A glove, Glazener, free from talc weighed 12 gm. (Size 7.)

	Talc in interior	Talc on exterior
a.	248 mg.	67 mg.
b.	284 mg.	34 mg.
c.	99 mg.	79 mg.
d.	170 mg.	117 mg. (19 mg. after beating out several times)
e.	209 mg.	194 mg. (42 mg. „ „ „ „ „
Average	202 mg.	98 mg.

In experimental animals it was observed that 100 mg. of talc powder produced massive adhesions in 10 rabbits. In another

10 animals extensive adhesions formed from 10 mg. talc; separation of these adhesions at a second operation caused death from shock in 3 animals.

From the average results obtained by weighing, two unwashed gloves will adhere 196 mg. talc powder. This is quite sufficient to cause extensive adhesions and enough to produce intestinal obstruction or talc granuloma.

Weed & Groves (1942) found that 22.5 % of gloves were perforated during operations. In two gloves the average weight of talc in the interior is 404 mg. So we can see the danger of a perforated glove, particularly if the tip is torn.

Talc is not only dangerous in abdominal operations but must also be eliminated at other operations. In Chapter 8 H, we can read records of talc granulomata which occurred in the lip and in abdominal wounds.

Talc is the most treacherous irritant in the peritoneal cavity. It may cause adhesions within a week, or may do so after many weeks. It may delay wound healing as seen in original experiments Group 6. It may penetrate the serosa of intestine, liver, fallopian tube or any surface covered by serosa. Finally, talc granuloma may be seen many years later when the talc has been forgotten. In these cases it simulates carcinoma.

K 285 Surgical glove powder. (Boots.)

In original experiments Group 8, it was shown that this powder is absorbed and causes no adhesions. This powder should replace talc as a lubricant for surgical gloves without an further consideration. Washing surgical gloves powdered with talc is an insufficient precaution. Talc must be eliminated.

F. *The Physiological Cause or The Inherent Tendency.*

The inherent tendency of some experimental animals and some human beings to form more fibrous tissue in response to injury than others, can not be overlooked.

Hertzler (1921) mentioned this tendency as a cause of adhesion formation, and showed that the formation of fibrous tissue can proceed beyond the body's need.

Boys (1942) in considering the prophylaxis of adhesions, thought that some individuals have a tendency to develop adhesions.

Lehman (1940) found the formation of adhesions in the peritoneum of patients who presented keloid abdominal scars. He called it a "fibroblastic diathesis."

In experimental animals it is more than obvious that in some animals a greater number, and denser adhesions are formed than in others under the same conditions.

It seems as if the physiological response in the formation of fibrous tissue is more sensitive to stimuli in these cases, and continues beyond the normal requirements for the protection of tissues.

Discussion of the treatment.

Before original methods of treatment are described, the most effective methods that were used in the past are briefly discussed.

1. *Amniotic fluid.*

This preparation was investigated by Johnson in 1928. In experimental animals 30 % of animals were completely protected. In his own estimation the effectiveness of amniotic fluid was 70 %.

The results are not sufficiently encouraging to apply this preparation in clinical cases.

2. *Pepsin and Trypsin.*

Yardumian and Cooper (1934) investigated pepsin experimentally. Their best results were 25 % cures in animals.

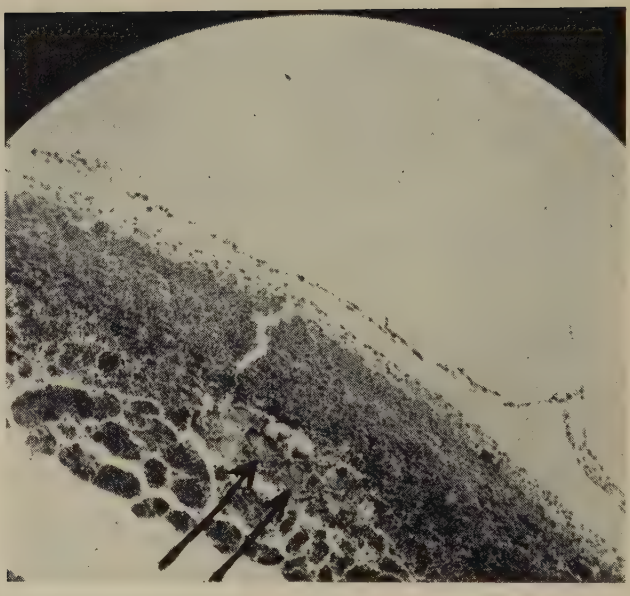
Ochsner and Garside (1932) tried trypsin in animals. Traumatized animals showed 9.09 % adhesions after treatment. Reformed adhesions which were divided at operation and treated with trypsin, showed that 42.28 % of animals were free from adhesions.

The results were not convincing.

3. *Papaine.*

Ochsner and Garside (1932) found 90.9 % satisfactory results with papine in experiments. In clinical cases they found 94.5 % satifactory results.

Elliott and Meleney (1937) treated 34 cases with papaine, and 38 cases were kept under observation as controls. They found very little difference between treated and untreated cases.



This section shows serosa, pus, and talc particles at points of arrows.

The same section. Talc particles seen under polarized light.

.4 *Streptokinase and Streptodornase.*

Tillett et al. (1950) found that these agents were ineffective in the prevention of adhesions.

5. *Heparin.*

Chandy (1950) proved that heparin did not prevent adhesions in the rat under a variety of conditions.

6. *Cortisone.*

Ragan (1950) and Spain (1950) found that cortisone treatment delays wound healing. Microscopic examination showed suppression of the fibroblast and all elements of connective tissue.

Hyaluronidase.

Thomas, Chandy et al. (1950) found that adhesions developed in 76 % when traumatized animals were treated with hyaluronidase, and 89 % in controls.

Connolly and Richards (1951) did further experiments and found that when adding this enzyme to talc as trauma, no adhesions formed in dogs. After division of adhesions produced by talc, they found 1000 units in one application insufficient to prevent adhesions in two dogs. In 5 dogs they found no adhesions after the application of 2000 units. They found no delay in the healing of anastomoses.

They treated 14 clinical cases with hyaluronidase after obstruction due to adhesions. Of these, 12 cases showed no symptoms afterwards, and were followed from 3 to 14 months postoperatively. Two cases obstructed 7 and 30 days after operation. Their dosage used in these 14 cases was 6000 units disolved in 20 cc. isotonic saline.

Connoly and Richards attribute the two clinical failures to insufficient dosage, and suggested that 10 to 12.5 thousand units would probably be necessary to prevent adhesions in surgical cases.

There is no doubt that we must credit these two workers for their most valuable observations. From their results we see the necessity of high dosage.

When judging their results we must ask:

1. What was their exact weight of talc used as trauma?

2. What distribution of talc deposits were found in the peritoneum after treatment?
3. Would it be possible to prevent adhesions in a larger series, particularly with talc trauma, still giving just one treatment?
4. Were adhesions to the interior of the wound also taken into consideration, or only intestinal adhesions?

In original experiments it was found essential to distinguish between intestinal adhesions and adhesions to the wound.

Adhesions to the wound were found in 6 out of 17 animals when talc was used as trauma, in spite of treatment with hyaluronidase for 6 days.

In 12 rabbits that were traumatized mechanically no adhesions were seen from intestine to wound, but in one animal a thin, long thread was seen which was counted as an adhesion.

Talc is treacherous in behavior and should be avoided in all experiments as trauma. It also varies in time of production, and number of adhesions produced when used as trauma. It is an unnatural way of producing adhesions.

From a fairly large number of animals used, experience thus obtained suggests that the method of trauma for judging true results of treatment should be done by: scraping the serosa, or clamping, introducing infection or inserting a thick and hard drainage tube.

Adhesions so produced would represent the true types of adhesions we meet with in clinical cases.

The weight of talc on the exterior of two surgical gloves has been shown to be almost 200 mg. With this amount of talc in rabbits, the small intestine is so matted that separation would be impossible, or doing so would kill the rabbit.

In original experiments (Group 6) some adhesions were produced with 10 mg. of talc. After 14 days they were divided at a second operation. Six injections of hyaluronidase 2000 units were given. No recurrence occurred of the divided adhesions, but adhesions formed to the wound, in two of the seven animals.

Although the talc formed no adhesions to the unhealed wound it did so after 28 days.

This fact establishes strong criticism of the results of experiments where talc was used as trauma.

The dosage, number of treatments, and the material used are

of great importance. Hyaluronidase has no international standardization, and treatment may fail unless a preparation made from testicular extract is used.

One treatment is insufficient to prevent adhesion Six treatments did not make a great histological difference in healing when compared with controls. (See sections Group 12.)

Connolly and Richards thought that the most probable *mode of action of hyaluronidase* was by antagonising the hyaluronic acid secreted by the fibroblast.

Although this complies with its action, it does not explain how one treatment of the enzyme can act on the fibroblast. Hyaluronidase is effective for 24 hours only, as explained by Dr. Marie Stoppelman (1949).

The fibroblast only makes its appearance from the 3 rd. to the 5th. day after injury, and continues until fibrous tissue has replaced the fibrin. The fibroblast has therefore not yet appeared when one treatment has lost its effect, but 6 treatments could definitely act in this way.

The action is more likely to be found in:

a. Rapid absorption of the exudate.

b. Its enzyme action (simulating leucoprotease) in dissolving fibrin.

c. Suppresion of the fibroblast, probably in the way suggested by Connolly and Richards, although it is only slightly noticed on microscopic examination.

In spite of the mild suppression of the fibroblast, hyaluronidase has no retarding influence on the healing of sutured intestines. This was shown in the writers own experiments in Group 9.

Conolly & Richards (1951) reported similar findings on sections prepared from treated and untreated dogs. (See Chapter 8 K.)

Hyaluronidase should be forbidden in cases of peritonitis owing to spread of infection. (See six experiments Group 10.)

The Clinical Administration of Hyaluronidase.

Indications.

Adhesions should not be treated prophylactically. In an aseptic abdominal operation nothing should be inserted into the peritoneal

cavity to prevent the formation of adhesions, unless extensive areas of denuded serosa remain at the end of the operation.

Often adhesions will not form if serosa alone is removed, but if underlying tissue is also injured over considerable areas, prophylactic treatment should be seriously considered, as adhesions will form in 90 % cases.

On occasions extensive adhesions are seen at the first laparotomy, usually due to some previous intraperitoneal inflammation. All the adhesions should be carefully divided and treatment should follow.

The true indications for hyaluronidase treatment are:

1. In all laparotomies where many adhesions are found and adhesions are loosened.

2. In cases that require operation or repeated operations on account of adhesions and have had no hyaluronidase treatment. e. g. Obstruction.

3. In cases where denuded areas are seen, and the patient can be classified as one who falls under the "fibroblastic diathesis" group.

It must be remembered that treatment should never be given if sepsis of any type is detectable in the peritoneal cavity. The spreading action of hyaluronidase will not only cause a general peritonitis, but may cause generalized lesions.

In exceptional cases where the infection has been controlled by antibiotic treatment, temperature is normal, and septic exudation or pus can not be seen, treatment may be given. Any antibiotic may be mixed with hyaluronidase, and in these cases it would be wise to use the combination.

Dosage.

There seems to be no contra-indication to the instillation of high doses of hyaluronidase into the peritoneum. The dosage suggested is 8000 units (Benger) in 150 cc. isotonic saline. It is important to dilute the exudate, as this helps its absorption.

Connolly and Richards (1951) suggested that a dosage of 10 to 12.5 thousand units would probably be necessary, as their treatment with 6000 units was unsuccessful in 2 out of 14 cases. They used only 20 cc. as solvent, and gave only one treatment. We can imagine that greater success could be expected with 150 cc. as dilutant, and five more treatments at 24 hour intervals.

According to Hertzler (1935), if the amount of isotonic solution inserted into the peritoneum does not exceed 10 % of the body weight, over 70 % is absorbed within two hours.

When hyaluronidase is added, the rate of absorption is greatly increased.

The volume of the peritoneal cavity of a 2 kgm. rabbit is 200 cc. when filled completely. In these animals 5 cc. solution was effective.

The volume of the human peritoneal cavity when filled completely probably varies. Dr. P. S. M. Kop (1948) in his work at Groningen on peritoneal dialysis in uraemia, states that 2000 cc. of fluid can be inserted into the peritoneal cavity. In ascites the peritoneal fluid may exceed the volume of 2000 cc.

Only one patient with extensive adhesions was treated at the Leiden University Hospital. A volume of 250 cc. caused discomfort on two occasions during the first three days, but 150 cc. which was given on two occasions, did not cause the slightest disturbance.

We must use the maximum volume of dilutant, as we must dilute the exudate. It seems as if 150 cc. is very well tolerated and this is the volume suggested.

Technique.

A. *First Method.*

The hyaluronidase, 8000 Benger units, is added to 150 cc. isotonic saline in a small vacolitre. This is heated in a basin of warm water up to 40° C., and is checked by a water thermometer.

Novocaine 5 cc. is injected into a site near the umbilicus. (The parietal peritoneum is more adherent to the abdominal wall round about the umbilicus.) The stitches (inserted over a swab at operation see figs. d. & e.) are then used to elevate the abdominal wall, and a fairly thick, short bevelled needle is inserted through the anaesthetized area. The needle is best left on a 10 cc. syringe

The clinical administration of intraperitoneal Hyaluronidase Solution. First Method.

At operation two silk sutures one inch apart are inserted over rolled gauze as shown in Fig. 1. The sutures must pass through the parietal peritoneum, and are inserted below the umbilical level.

Fig. d.

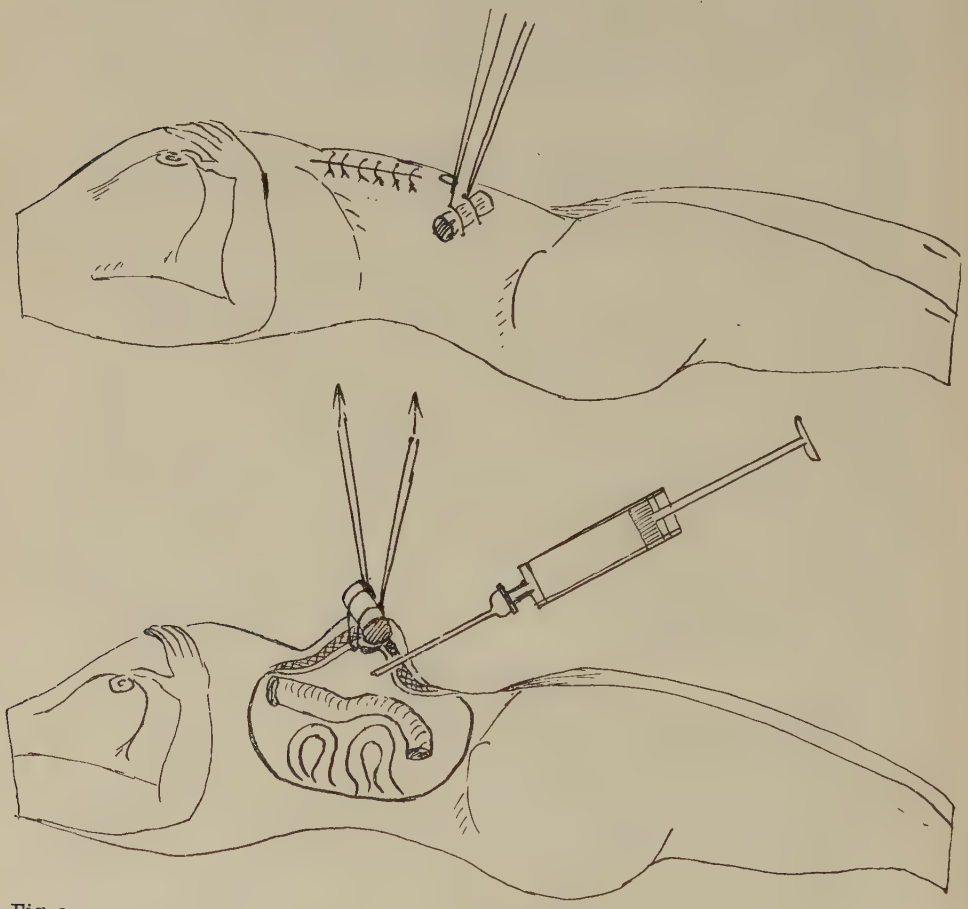


Fig. e.

To avoid puncture of intestine the abdominal wall (and peritoneum) is elevated by traction before procaine is injected into the peritoneum. Hyaluronidase solution may then be inserted while suture traction is maintained.

containing some of the heated solution, and the injection is made continuously while inserting the needle through the peritoneum with the intention to blow intestine away from the parietal peritoneum.

These precautions are necessary to avoid a perforation from the entering needle. Dr. Kop (1949) while performing dialysis, gained considerable experience in the insertion of intraperitoneal needles. He warns us about the danger of inserting a needle when meteorism or gross distension is present. He relates a case in which the intestine was perforated when meteorism was present. The perforation was repaired under local anaesthesia.

This occurred in only one of his 21 cases treated.

It is of great importance therefore, to examine the abdomen before treatment, and to be aware of the degree of distension before commencing such treatment.

Of the clinical cases treated, only one has been done by intraperitoneal injection. The others were injected through a small catheter stitched into the peritoneum.

Foreign bodies in the peritoneum should be avoided completely, and therefore this method is the one which would conform absolutely to our principles in treatment. The first treatment is best done at operation. The solution is poured directly on to the traumatized area. In this way the primary exudate is saturated with hyaluronidase solution, which will already abolish the sticky exudate, or first dangerous process in the formation of adhesions.

A problem of some magnitude arises in paracentesis of the peritoneum during distension. Distension can not be predicted beforehand. If it is gross, and lasts for some days, the fear of perforation of an intestine could demand interruption or even total discontinuation of treatment. Should treatment be delayed, or even omitted for one day, results would be very disappointing.

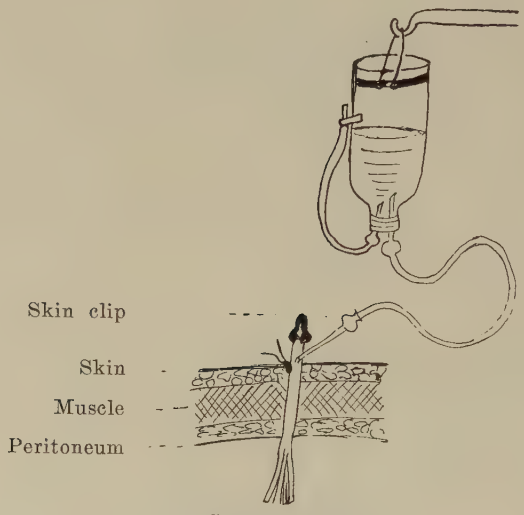
B. *Second Method.*

A small soft catheter or rubber tube is stitched into the peritoneum when the wound is closed, and held in position by a skin stitch. The part which enters the pertoneal cavity is split into four parts which gives it a fimbriated, movable, and soft effect.

The outer end is closed off with a skin clip, so that the injections that must follow can be made directly through the tube.

Although there is no clinical evidence as yet, there is strong experimental proof that this arrangement does not result in adhesion formation to the tube. (See experiments Group 6.)

This method offers a very simple and safe method of treatment and ensures that daily treatment can be given regardless of the presence of distension.



Second Method.

SUMMARY.

A review of the history and literature of adhesions has been given, from the earliest times up to the present day.

The development, physiology and anatomy of the peritoneum has been outlined.

Intestinal obstruction, the frequency of adhesions and the histological genesis of adhesions have been studied.

The causation of adhesions has been reviewed, and all the experimental and clinical methods in the prevention of adhesions have been studied in detail.

Original work, mostly experimental on 94 animals, and a few clinical cases are recorded.

Finally the principle in treatment of abdominal adhesions has been established, and intraperitoneal hyaluronidase treatment for six days has been shown to prevent primary and divided adhesions in all animals if treated according to the established method.

BIBLIOGRAPHY.

Adler, I. & Meltzer, S. J. (1896). Jour. Exper. Med. **1**. 482.

Antopol, W. (1933). Arch. Path. **16**. 326.

Austin, C. R. (1948). Nature **162**. 63.

Baar, F. (1953). B. M. J. May 23, 1146.

Bainbridge, W. S. (1913). Amer. J. Surg. **27**. 364.

Baum, F. (1894). (quoted by Ochsner). J. Am. M. Ass. **23**. 242.

Bichat, (1771—1802). Parisian Physician Extraordinary.

Bogart, Leon M. (1937). Arch. Surg. **34**. 129.

Bolton, C. (1921). J. Path. & Bact. **24**. 429.

Boys, F. (1942). Surgery **11**. 118.

Boys, F. & Lehman, E. P. (1943). Ann. Surg. **118**. 612.

Bratton, A. C. & Marshall, E. K. Jnr. J. Biol. Chem. **128**. 537.

Bruce, J. & Walmsley, R. (1939). Manual of Surgical Anatomy Ed. 5. p. 331. Publ. Oxford Univ. Press. London. Humphrey Milford.

Burgess, A. H. (1929). Lancet, April 27.

Cantacuzene, J. & Vles, F. (1923). (quoted by Steinberg) Arch. de Physique Biol. **3**. 5.

Cantacuzene, J. (1931). (quoted by Steinberg) Arch. Roumaines de Path. Exper. et de Microbiol. **4**. 173.

Carslaw, R. B. (1928). Brit. Jour. Surg. April, 545.

Carson, H. W. (1923). Lancet **1**. 1035.

Chain, E. & Duthie, E. S. (1940). Brit. J. Exp. Path. **21**. 324.

Chandy, J. (1950). Arch. Surg. **60**. 1151.

Chandy, J. & Rhoads, J. E. (1946). Fed. Proc. V. **5**. 218.

Chao, Yi-Chang, Humphries, S. & Penfield, W. (1946). B. M. J. **1**, 517.

Chester, S. T., Bell, H. G. & McCorkle, H. J. (1949). Surg. Gynaec. & Obstr. **89**. 605.

Christopher, F. C. (1939). Textbook of Surgery. Chap. 27. p. 1146. W. B. Saunders & Co. Philad.

Conolly, J. E. & Richards, V. (1951). Surgical Forum. (Proc. Clinic. Congress of Amer. Coll. Surg.) p. 85.

Cornil, V. & Carnot, P. (1898). Presse Med. No. **84**. 217. (quoted by B. Steinberg, 1944).

Coudry, E. V. (1934). Textbook of Histology. p. 235. Publ. Lea & Ferbiger, Philad.

Cunningham, R. S. (1927). Am. J. Physiology, **82**. 59.

Crutcher, R. R., Daniel, R. A. Jnr., & Billings, F. T. (1943). Ann. Surg. **117**. 677.

Davis, L. & Aries, L. J. (1937). Surgery **2**. 877.
Debowski, T. (1888). (quoted by Ochsner). Arch. F. Klin. Chir. **37**. 745.
Demidova, P. N. (1940). (quoted by Coombs, J. N.). The Encyclopedia of Medicine. Publ. F. A. Davis & Co. Philad.
Duff, G. L. Personal communication to F. Boys Sept. (1939).
Duran-Reynals, F. (1929). J. Exp. Med. **50**. 327.
Duran-Reynals, F. (1933). J. Exp. Med. **58**. 161.
Duran-Reynals, F. (1938). Proc. Soc. Exp. Biol. & Med. **38**. 763.
Duran-Reynals, F. (1942). Bact. Rev. **6**, 197.
Eiseman, B., Seelig, M. G. & Womack, N. A. (1947). Ann. Surg. **126**. 820.
Elliott, Egerton R. H. & Meleney, Frank L. (1937). Surgery **1**. 785.
Faulds, J. S. (1935). J. Path. Bact. **41**. 129.
Feinberg, R. (1937). Arch. Path. **24**. 36.
Flesch-Tebesius, quoted by Ochsner, (1932).
Frans, K. (1902). (quoted by Ochsner.) Ztschr. f. Geburtsch u. Gynaec. **47**. 64.
Gay, F. B. et al. (1935). Agents of Disease and Host Resistance. Chap. I. Publ. Charles C. Thomas. Baltimore.
Goddesden, John of, (1314). Rosa Anglica. (Obtainable at R. C. S. library London.)
Green, W. L. (1946). J. Indiana State Med. Ass. **39**. 634.
Gundermann, W. (1913). Beitr. z. Klin. Chir. **84**. 587.
Halsted, W. S. In Memoriam: Willem Stewart Halsted by Malas, R., Miller, R. T. & Hever, G. J. (1925). Arch. Surg. **10**. 293.
Hamilton, W. J., Boyd, J. D. & Mossman, H. W. (1952). Human Embryology. Ed. 2. p. 214. Publ. W. Heffer & Sons Ltd. Cambridge.
Harbison, S. P. & Key, J. A. (1942). Arch. Surg. **44**. 22.
Hebra & Unna (1892). quoted by Sollman, T. (1934). A Manual of Pharmacology. p. 205. Ed. Philad. W. B. Saunders & Co.
Heinz, R. (1901). München Med. Wchnschr. **48**. 585.
Hertzler, A. E. (1919). The Peritoneum. Vol. 1. Chap. 7. p. 317. C. V. Mosby Co., St Louis.
Hertzler, A. E. (1921). The Peritoneum, St. Louis. Publ. C. V. Mosby Co.
Hertzler, A. E. (1923). Surg. Clin. N. Amer. **2**. 1477.
Hertzler, A. E. (1935). Surgical Pathology of the Peritoneum. (Monographs on Surg. Path.) Publ. J. B. Lippincott Co. Philad.
Higgins, G. M. & Graham, A. S. (1929). Arch. Surg. **19**. 435.
His, W. (1885). Anatomie Menschlicher Embryonen III. Zur Geschichte der Organe. Vogel, Leipzig.
Hunter, John. (1728—1793). (Books at R. C. S. library London). Publ. Clowes & Sons, Charing Cross. Chap. 3. p. 393.
Jackson, H. C. (1941). Ann. Surg. 113. 1069.
Jackson, H. C., & Coller, F. A. (1942). J. A. M. A. 118. 194.
Johnson, H. L. (1927). Surg. Gynaec. & Obstr. **45**. 612.
Johnson, H. L. (1928). N. Eng. J. Med. **199**. 661.
Johnson, H. L., Coonse, L. K., Hazard, J. B., Forcee, P. S. & Aufranc, O. (1937). Surg. Gynaec. & Obst. **62**. 171.

Jones, D. F. & McClure, W. L. (1929). in Lewis, Dean: Practice of Surgery. Vol. 7. Chap. 8. p. 49. Publ. W. F. Prior Co, Inc.
Kirby, C. K., Eckenhoff, J. E. & Looby, J. P. (1949). Surgery. **25**. 101.
Kop, P. S. M. (1948). Thesis, Peritoneal Dialysis, Groningen.
Krook, S. S. (1947). Acta. Chir. Scand. Sup. **125**. p. 13
Kubota, T. (1922). Japan Med. World. **11**. 226.
Lacey, T. J. (1930). Ann. Surg. **92**. 281.
Ladwig, A. (1928). Arch. Klin. Chir. **151**. 1.
Laennec, René. (1781—1826). Surgean & Anatomist.
Laird, G. J. & Stavern, H. (1942). Cal. & Western Med. **56**. 293.
Lee, C. M. & Lehman, E. P. (1947). Surg. Gynaec. & Obstr. **84**. 689.
Lehman, E. P. & Boys, F. (1940). Ann. Surg. **111**. 227.
Lehman, E. P. & Boys, F. (1940). Ann. Surg. **111**. 427.
Lehman, E. P. & Boys, F. (1940). Ann. Surg. **112**. 969.
Lehman, E. P. & Boys, F. (1941). Ann. Surg. **43**. 933.
Lehman, E. P. & Boys, F. (1942). Surgery **12**. 236.
Lyons, C. & Burbank, C. (1942). Surg. Gyn. & Obstr. **74**. 571.
MacKey, W. A., & Gibson, J. B. (1948). Brit. Med. Jour. **1**. 1077.
Mall, E. P. (1910). Coelom and Diaphragm, in Manual of Human Embryology. (Kerbel & Mall) 1. Publ. Lippincott, Philad. & London.
McClean, D. (1936). J. Path. & Bact. **42**. 477.
McGregor, A. Lee. (1940). A Synopsis of Surg. Anatomy. Ed. 4. p. 57. Publ. John Wright & Sons Ltd. Bristol.
Meyer, K. & Palmer, J. W. (1934). New York. J. Biol. Chem. **107**. 627.
Morgagni. (1761). De Sedibus et Causis Morborum. Vol 1. Letter No. **35**. p. 165.
Muller, R. S. & Thompson, J. E. (1942). J. A. M. A. **118**. 189.
Muller, G. (1929). Surg. Gynaec. & Obstr. **48**. 817.
Muller, G. P. & Rademaker, L. A. (1933). Arch. Surg. **26**. 280.
Ochsner, A. & Garside, E. (1932). Surg. Gynaec. & Obstr. **54**. 338.
Ochsner, A. & Mason, F. (1928). Proc. Soc. Expr. Biol. & Med. **25**. 524.
Ochsner, A. & Storck, A. (1932). Yearbook of Gen. Surg. p. 325.
Ochsner, A. & Storck, A. (1936). Ann. Surg. **104**. 736.
Odell, R. T., Key, J. A. & Taylor, L. W. (1951). Surg. Forum. Proc. Clin. Congress of Amer. Coll. Surg. p. 524.
Opie, E. L. (1910). Inflammation. Harvey Lectures. Philad. & London. J. B. Lippincott Co.
Parkinson, J. (1812). Pupil to John Hunter.
Payr, E. (1913). Über Postoperative und Spontane Adhäsionen in der Bauchhoele. Verhandl. d. Gesellsch. Deutsch. Naturf. u. Aerzte. p. 384.
Payr, E. (1914). Zbd. Chir. **1**. 99.
Payr, E. (1914). Zentralbl. f. Chir. **41**. 99.
Payr, E. (1914). J. A. M. A. **62**. 171.
Payr, E. (1922). Deutsche Med. Wschr. **48**. 715.
Payr, E. (1922). Zentralbl. f. Chir. **49**. 2.
Pope, S. (1914). Ann. Surg. **59**. 101.

Postlethwaite, R. W. et Al. (1949). Surgery. **25**. 22.
Ragan, C., Howes, E. L., Plotz, C. M., Meyer, C., Blunt, W. J. & Lattes, R. (1950). Bull. New York Acad. Med. **26**. 251.
Ravdin, I. S., Rhoads, J. E. & Lockwood, J. S. (1940). Ann. Surg. **111**. 53.
Rea, C. E. & Wagensteen, O. H. (1933). Proc. Soc. Exp. Biol. & Med. **31**. 1060.
Reichert, F. L., Gerbose, F. & Halford, F. S. (1939). Ann. Surg. **110**. 669.
Rhodes, J. (1949). Ann. Surg. **130**. 478.
Richardson, E. H. (1911). Ann. Surg. **54**. 758.
Robbins, C. F., Brunschwig, A. & Foote, F. W. Jnr. (1949). Ann. Surg. **130**. 466.
Roberts, G. B. S. (1947). Brit. J. Surg. **34**. 417.
Ross, W. B. & Lubitz, J. M. (1949). Ann. Surg. **130**. 100.
Rubin, I. C. (1911). Surg. Gynaec. & Obstr. **12**. 117.
Rutenburg, H. M., Seligman, A. M. & Fine, J. (1949). J. of Clin. Investigation. **28**. 1105.
Scheinberg, S. R. & Saltzstein, H. C. (1951). Arch. Surg. **63**. 413.
Schwartzman, J. et al. (1948). J. Pediat. **33**. 267.
Seelig, J. (1943). J. Amer. Med. Ass. **123**. 950.
Seeman, G. (1931). Histobiologie der Lungenalveoli. Publ. Fischer, Jena.
Senn, N. (1888). quoted by Ochsner. Ann. Surg. **7**. 99.
Shattock, S. G. (1916). Proc. R. Soc. Med. **10**. Sect. of Path. 6.
Shattock, S. G. (1916). Proc. R. Soc. Med. Path. Sect. 9.
Silvester, C. F. (1911). Amer. J. Anat. **12**. 447.
Simer, P. H. (1934). Amer. J. Anat. **54**. 203.
Simer, P. H. (1937). Surg. Gynaec. & Obstr. **64**. 872.
Singleton, A. O., Rowe, E. B. & Moore, R. M. (1952). Amer. Surg. **18**. 789.
Spain, D. M., Molomut, N. & Haber, A. (1950). Amer. J. Path. **26**. 710.
Sprague, R. G., Power, M. & Mason, H. L. (1950). J. A. M. A. **144**. 1341.
Steinberg, B. (1944). Infections of the Peritoneum. p. 59. Ed. I. Publ. Paul Hoeber, N. York & London.
Stewart, G. N. (1918). Text Book of Physiology. Ed. 8. Publ. William Wood & Co., New York.
Stoppelman, Marie R. H. (1949). Nederlands Tijdschrift voor Geneeskunde. **4**. 4320.
Sutton, H. B. (1942). J. Amer. Med. Ass. **119**. 559.
Sweet, J. E., Chaney, R. H. & Willson, H. L. (1915). Ann. Surg. **61**. 297.
Tillett, et al. Quoted by Thomas, Green & Rhoads (1950).
Thomas, J. W., Green, J. W. & Rhoads, J. E. (1950). Surgical Forum. **125**.
Thomas, J. W., Jackson, G., Clifton, P., Chandy, J. & Rhoads, J. E. (1950). Proc. Soc. Exp. Biol. & Med. **74**. 497.
Thomas, J. W. & Rhoads, J. E. (1950). Arch. Surg. **61**. 565.
Thompson, J. E., Brabson, J. A. & Walker, J. M. (1941). Surg. Gynaec. & Obstr. **72**. 722.
Throckmorton, T. D. (1941). Proc. Staff. Meet. Mayo Clinic. **16**. 423.
Throckmorton, T. D. (1942). Surgery. **12**. 906.
Trusler, H. M. (1931). Arch. Surg. **22**. 983.

Wagensteen, O. H. (1937). Intestinal Obstruction. Ed. 1. Publ. C. Thomas, Illinois.
Wagensteen, O. H. (1942). Intestinal Obstruction. Ed. 2. Publ. C. Thomas, Illinois.
Walker, W. (1948). Brit. Med. J. **1**. 1079.
Walton, R. P. (1930). J. Pharm. & Exp. Therapy. **40**. 403.
Walton, R. P. (1931). Exper. Therap. **43**. 387.
Ward, G. G. (1901). Amer. J. Obstr. **43**. 753.
Warren, S. (1928). Effects of Amniotic Fluid on Serous Surfaces. Trans. of Amer. Coll. of Physic. Washington. D.C.
Weed, L. A. & Groves, L. J. (1942). J. Surg. **75**. 661.
Wereschinski (1924). quoted by S. S. Krook.
Yardumian, K. & Cooper, D. H. (1934). Arch. Surg. **29**. 264.